IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL SRL, and ORTHO-MCNEIL, INC.,	:	
Plaintiffs,	:	C.A. No. 07-255-JJF
v.	:	REDACTED PUBLIC VERSION
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	:	
Defendants.	:	

DECLARATION OF ROBERT E. COLLETTI IN SUPPORT OF DEFENDANTS' MOTION TO COMPEL PRODUCTION OF FOREIGN DOCUMENTS

I, Robert E. Colletti, declare pursuant to 28 U.S.C. § 1746 that:

1. I am a partner with the law firm of Frommer Lawrence & Haug LLP located at 745 Fifth Avenue, New York, New York 10151 and am counsel to Par Pharmaceutical, Inc. and Par Pharmaceutical Companies, Inc., (jointly "Par") in this action.

2. I make the following declaration in support of Defendants' Motion to Compel Production of Foreign Documents.

3. Exhibit A is a true and correct copy of a February 27, 2008 letter from Sona De to Robert E. Colletti.

4. Exhibit B is a true and correct copy of a March 3, 2008 letter from Robert E. Colletti to Sona De.

5. Exhibit C is a true and correct copy of a March 7, 2008 letter from Thomas A. Wang to Robert E. Colletti.

6. Exhibit D is a true and correct copy of an English Translation of DE 4315525 bearing production numbers PUR0375443 – PUR0375452.

7. Exhibit E is a true and correct copy of U.S. Patent No. 6,254,887 bearing production numbers PUR0533352 – PUR0533364.

8. Exhibit F is a true and correct copy of the Patent Assignment Abstract of Title for U.S. Patent No. 6,254,887.

9. Exhibit G is a true and correct copy of the Settlement Agreement between Mundipharma Laboratories GmbH, Euro-Celtique S.A., Napp Pharmaceutical Group Limited, Asta Medica AG, and Temmler Pharma GmbH, dated March 21, 1999, bearing production numbers DDK013902 – DDK013926.

10. Exhibit H is a true and correct copy of an Information Disclosure Statement bearing production numbers PUR0536000 – PUR0536002.

11. Exhibit I is a true and correct copy of the Statutory Declaration of Kenneth Frederick Brown before the Commonwealth of Australia bearing production numbers PUR0912025 – PUR0912050.

12. Exhibit J is a true and correct copy of the Counter Statement by Euro-Celtique S.A. in response to the opposition of Grunenthal GmbH against New Zealand Patent Application 260,408 bearing production numbers NAPP026588 – NAPP0267600.

13. Exhibit K is a true and correct copy of a February 5, 2008 letter from Robert E. Colletti to Sona De.

14. Exhibit L is a true and correct copy of a February 11, 2008 letter from Robert E. Colletti to Sona De.

15. Exhibit M is a true and correct copy of a February 21, 2008 letter from Robert E. Colletti to Sona De, Richard D. Kirk, Robert J. Goldman, and Mary W. Bourke.

16. Exhibit N is a true and correct copy of an excerpt from the Family Legal Status Report for U.S. Patent No. 6,254,887.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: March 25, 2008

Robert E. Colletti

Robert E. Colletti

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on March 25, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

Jack B. Blumenfeld, Esquire
Rodger D. Smith II, Esquire
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P.O. Box 25130
Wilmington, DE 19899-5130

Mary W. Bourke, Esquire
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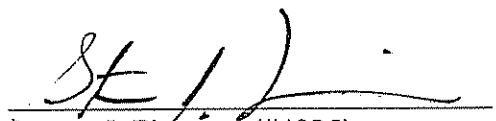
I hereby certify that on March 25, 2008, I have sent by Electronic Mail, the foregoing document to the following non-registered participants:

Robert J. Goldman, Esquire
Ropes & Gray LLP
525 University Avenue
Suite 300
Palo Alto, California 94310

Richard A. Inz
Sona De
Ropes & Gray LLP
1211 Avenue of the Americas
New York, New York 10036



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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on April 8, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

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Richard A. Inz
Sona De
Ropes & Gray LLP
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New York, New York 10036

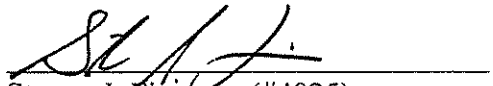

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EXHIBIT A

ROPES & GRAY

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February 27, 2008

Sona De
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BY ELECTRONIC MAIL

Robert E. Colletti, Esq.
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

Re: *Purdue et al. v. Par Pharmaceutical et al.*

Dear Rob:

I write in response to the questions you have raised regarding the Napp and Purdue document production in your letters of February 5, 11, and 21.

Abandoned U.S. patent applications 09/239,092 and 09/507,806

Abandoned applications 09/239,092 and 09/507,806 are not relevant to any claim or defense asserted in this action. While these are continuations-in-part of the application that issued as the '887 patent, neither of these abandoned applications appear on the face of the '887 patent-in-suit, nor do they have any relation to the issuance of the '887 patent itself. These applications list different named inventors and had claims directed to avoiding non-linear pharmacokinetics of plasma tramadol concentrations and/or supersaturation of hepatic enzymes by tramadol, which is different than the dissolution rates of the '887 patent. Moreover, both these applications were abandoned before there was any substantive prosecution by the applicants. Application 09/239,092 was filed on January 27, 1999 and abandoned on December 22, 1999, but there was no substantive prosecution of that application during that time. Application 09/507,806 was filed on February 22, 2000 and abandoned after November 14, 2002, however, it does not appear that the applicants responded to any office actions during its pendency.

In any event, we note that your February 21st letter acknowledges that the file histories for these two abandoned applications were included in the documents produced by Davidson, Davidson & Kappel.

Foreign patent prosecution histories

Foreign counterpart patents and their respective prosecution file histories, other than the four foreign priority applications listed on the face of the '887 patent-in-suit (the "foreign priority applications"), are not relevant to any claim or defense in this lawsuit. Foreign counterpart patents involve different claims and are prosecuted under the laws of their respective tribunals. Accordingly, they have no bearing on the '887 patent-in-suit. To the extent that Par believes otherwise, foreign patents and their prosecution histories are publicly available documents that Par can obtain for itself, at comparable burden and expense to what it would cost Purdue and Napp to collect and process the documents.

Because the '887 patent-in-suit cites four foreign priority applications, however, Purdue and Napp have produced non-privileged documents in its possession related to the prosecution of those four foreign priority applications.

Expert report of Professor Alexander Florence

Professor Florence's expert report was submitted by Napp to a foreign tribunal in connection with foreign litigation that does not involve the '887 patent-in-suit. Accordingly, his expert report is not relevant to any claim or defense in this action, and unlikely to lead to any admissible evidence. Moreover, court filings are publicly available documents that Par can obtain itself.

In any event, we note that your February 21st letter acknowledges that the expert report of Professor Florence requested in your February 5th letter was included in the documents produced by Davidson, Davidson & Kappel.

Grunenthal/Searle license

The July 8, 1994 Grunenthal/Searle tramadol license agreement requested in your February 5th letter appears to be an agreement between two non-parties to this litigation. It is also unclear based on the amendment to that license produced by Napp whether the July 8, 1994 license even involved a controlled release formulation of tramadol, or how a license between two third-parties would be otherwise relevant to any claim or defense in this action. In any event, we have conducted a reasonable search of the documents we collected from Napp and have not been able to locate a copy of this license to date.

Foreign litigation

Foreign litigation before a foreign tribunal is not relevant to any claim or defense in this action. Specifically, the foreign priority applications listed on the face of the '887 patent-in-suit were not at issue in either litigation cited in your February 5th letter (*Napp Pharmaceutical Group Ltd. v. Asta Medica Ltd. UK* or *Temmler Pharma GmbH v. Euro-Celtique*

S.A.). Moreover, it is highly burdensome for Napp to collect, review, and produce voluminous litigation and opposition files from outside counsel across the world that have no bearing on the '887 patent-in-suit -- especially considering that court filings are publicly available documents that Par can obtain itself. The non-privileged documents having any relevance to this litigation which Purdue and Napp have produced are voluminous as it is. There is no sound basis in law to further inject documents from numerous unrelated foreign litigations into this case.

To the extent that documents related to foreign litigations or oppositions were submitted to the U.S. Patent and Trademark Office and made of record during the prosecution of the '887 patent-in-suit, however, such documents have been produced from the files of Davidson, Davidson & Kappel. This includes the supplemental expert report of John Tasker Fell, which was submitted by third-party Asta.

Please call me if you would like to discuss any of this further.

Sincerely,

Sona De

SD:amp

EXHIBIT B

FROMMER LAWRENCE & HAUG LLP

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March 3, 2008

VIA ELECTRONIC MAIL
AND FIRST-CLASS MAIL

Sona De, Esq.
Ropes & Gray LLP
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New York, New York 10036

Re: *Purdue et al. v. Par Pharmaceutical et al.*
FLH Reference No. 540572-521

Dear Sona:

This letter responds to your February 27, 2008 letter and addresses the foreign patent prosecution histories corresponding to U.S. Patent No. 6,254,887 ("the '887 patent"), the foreign litigation documents related to controlled-release tramadol, and the license agreement between Searle and Grunenthal.

Foreign Patent Prosecution Histories

With respect to the foreign patent prosecution histories, plaintiffs contend that foreign counterpart patents and their respective prosecution histories, which are not listed as priority documents on the face of the '887 patent, are irrelevant. We disagree.[1]

The prosecution histories of patents and applications corresponding to the '887 patent are relevant to this litigation and should be produced. The Federal Circuit has expressly acknowledged the relevance of evidence from foreign patent offices. *See Caterpillar Tractor Co. v. Berco, S.p.A.*, 714 F.2d 1110, 1116 (Fed. Cir. 1983) ("[W]hen such matters [instructions to foreign counsel and a representation to foreign patent offices] comprise relevant evidence they must be considered."); *see also Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n*, 109 F.3d 726, 733 (Fed. Cir. 1997) ("representations made to foreign patent offices are relevant to determine whether a person skilled in the art would consider butanone or other ketones to be interchangeable with acetone in [the patentee's] claimed N-alkylation reaction"). Relying on

[1] To the extent your letter implies the file histories for the foreign priority document were produced, please identify them by production number.

this case law Judge Farnan denied a motion to exclude a decision of the Austrian Patent Office and held: "Because the Court cannot conclude that this evidence is entirely irrelevant, and Pfizer has not advanced any grounds under *Rule 403* justifying its exclusion, the Court will admit the evidence and address Pfizer's concerns in terms of the weight to be afforded this evidence." *Pfizer Inc. v. Ranbaxy Labs., Ltd.*, No. 03-209, 2005 U.S. Dist. LEXIS 34901, at *11 (D. Del. Dec. 22, 2005). Likewise, in *Liposome Co. v. Vestar, Inc.*, No. 92-332, 1994 U.S. Dist. LEXIS 19325, at *40 (D. Del. Dec. 20, 1994), the Court held that statements made to a foreign Patent Office are relevant as evidence of how the patentees "had in fact read the words of the claim at a time when it was not looking at them as a necessary step in building a claim for relief that moves from complaint to recovery. [Patentee's] prior statements are also relevant as they are evidence of how one skilled in the art would interpret the words in the patent."

The foreign prosecution histories in this case are relevant to claims of noninfringement and invalidity in this case. Plaintiff's statements regarding controlled release tramadol to foreign patent offices will shed light on prior art and the patentees' understanding of the scope of the alleged invention prior to litigation.

Foreign Litigation

We disagree with plaintiffs' position that litigation of corresponding foreign patents directed to control release tramadol is irrelevant to a claim or defense in this action. Purdue's corresponding foreign patent EP 624 366, which is a foreign counterpart to the '887 patent, was revoked. The evidence and facts relied upon by the foreign patent court for the revocation of EP 624 366, and the positions taken by plaintiffs, must be produced. Moreover, the German and UK controlled release tramadol litigations focused on the same issues contested in this case. Plaintiffs cannot simply ignore litigation involving controlled release tramadol in foreign jurisdictions. "I do not read the Federal Circuit's cases as compelling courts of the United States to ignore an informed decision rendered abroad. . . If a foreign court renders a judgment on a question of fact with significance in each system of law, there is no reason not to take over that decision. . . ." *Vas-Cath, Inc. v. Mahurkar*, 745 F. Supp. 517, 526 (D. Ill. 1990), *rev'd* on other grounds, 935 F.2d 1555 (Fed. Cir. 1991). As such, the evidence submitted and the decisions of foreign courts concerning the foreign counterparts to the '887 patent, are relevant and properly discoverable in this case.

Grunenthal/Searle License

The July 8, 1994 New Tramadol License Agreement between Grunenthal and Searle is relevant to understanding the produced amended agreement in which Napp will be providing the "Substance (as defined in the Agreement)" to Searle. (*See* NAPP044052). Plaintiffs' reasoning that it is "unclear" whether the agreement involved a controlled-release formulation of tramadol is not a proper basis for withholding the requested documents. The original agreement is

relevant to understanding the produced amendment, which is for a controlled-release tramadol formulation. Please produce the July 8, 1994 Agreement. If this agreement cannot be located please let us know and explain the search effort to locate the document.

Please produce the requested foreign counterpart patents and their prosecution histories and the foreign litigation documents by Friday, March 7. Otherwise, we will seek the assistance of the Court.

Sincerely,

Robert E. Colletti

Robert E. Colletti

Encl.
cc: Robert J. Goldman, Esq.
Mary W. Bourke, Esq.
Richard D. Kirk, Esq.
Frederick L. Cottrell, Esq.

EXHIBIT C

ROPES & GRAY

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March 7, 2008

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VIA ELECTRONIC MAIL

Robert E. Colletti, Esq.
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

Re: *Purdue et al. v. Par Pharmaceutical et al.*

Dear Rob:

I write in response to your letter dated March 3, 2008 to Sona De, who is out of town, regarding Par's demand that Purdue and Napp collect and produce (1) publicly available files relating to over 30 additional foreign patent prosecution, foreign patent litigation, and oppositions, beyond the thousands of pages that Purdue, Napp, and its outside patent counsel have already produced; and (2) the license agreement between Grunenthal and Searle, which we previously told you that we cannot locate.

Documents related to foreign patent proceedings

Plaintiffs Purdue and Napp and third-party Mundipharma have already produced thousands of documents related to the prosecution of the U.S. patent in suit, its parent, and continuations, as well as the foreign patent applications to which the U.S. applications claim priority.[1] To the extent that such documents exist, are in Purdue or Napp's possession, and are not privileged, Par has them.

In addition, Purdue and Napp's outside patent counsel, Davidson, Davidson, and Kappel ("DDK"), has also produced over 13,000 pages of documents, approximately 6,000 pages of which relate to foreign patent proceedings. For example, documents from foreign proceedings were produced in the following production ranges:

DDK 3769-7529
DDK 9559-10718
DDK 11136-11996

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[1] These applications are GB 9324045, GB 9404544, GB 9404928, and DE 4315525.

DDK 12590-13628

In addition to the foreign applications that form the basis of the U.S. patent in suit, there have been at least four foreign litigations and foreign opposition proceedings involving at least seven opposers relating to other Purdue/Napp/Mundipharma applications relating to controlled-release tramadol. During the prosecution of the U.S. patent in suit, DDK disclosed these proceedings to the U.S. Patent and Trademark Office and provided evidence submitted in those proceedings to the PTO. These documents include art references, expert reports and affidavits submitted by Dr. Momberger, Prof. Florence, Ms. Malkowska, Dr. Fell, Dr. Posch, Dr. Beszedes, Dr. Budd, Mr. Oshlack, Dr. Roth, Dr. Winkler, and Dr. Smith, and other papers submitted by Napp, Asta Medica Group, Lannacher Heilmittel, Hexal, Arzneimittelwerk Dresden, Krewel Meuselbach, and Nycomed Danmark. All of these have been produced to Par.

What Par is requesting, however, goes beyond anything that was involved in the prosecution of the U.S. patent in suit or its foreign priority documents. As identified at the DDK deposition on March 5, there have been over 30 foreign prosecutions of Purdue/Napp/Mundipharma applications relating to controlled-release tramadol (*see, e.g.*, DDK 13919-922). These papers are publicly available. The burden of obtaining those papers is at least equal for Par and for Purdue and Napp. Indeed, the burden of Purdue and Napp collecting and producing those papers from the files of its foreign patent counsel is greater, because Purdue and Napp would have to sort privileged communications from non-privileged public documents.

In Purdue's and Napp's view, there is no sound reason for Par to impose this burden on Purdue, Napp, or Mundipharma.

The cases that you cite in your March 3, 2008 letter are inapposite. They stand for the unremarkable proposition that documents from foreign patent proceedings may be relevant in certain circumstances. They do not address whether a party must produce such documents when they are voluminous and equally available to the other party. *See* Rule 26(b)(2), Fed. R. Civ. P.

To the extent that Par wishes to collect documents from the remaining 30 foreign proceedings, it is free to do so. After obtaining those files, if Par has a more focused request for additional documents from any of those proceedings, Purdue and Napp will consider such a request.

Grunenthal/Searle license

As stated in Sona De's letter of February 27, 2008, we have been unable to locate a copy of the July 8, 1994 Grunenthal/Searle license that you requested. We have run searches on the documents and have found only the Amendment to the agreement that has already been

produced; however, we note that we have not completed the coding of all of our documents for electronic searching.

Regards,

Thomas A. Wang

TAW:amp

EXHIBIT D

REDACTED IN ITS ENTIRETY

EXHIBIT E

US006254887B1

(12) **United States Patent**
Miller et al.

(10) **Patent No.: US 6,254,887 B1**
(45) **Date of Patent: *Jul. 3, 2001**

(54) **CONTROLLED RELEASE TRAMADOL**

(75) Inventors: **Ronald Brown Miller**, Basel (CH); **Stewart Thomas Leslie**, Cambridge (GB); **Sandra Therese Antoinette Malkowska**, Cambridgeshire (GB); **Kevin John Smith**, Cambridge (GB); **Walter Wimmer**, Limburg (DE); **Horst Winkler**, Linter (DE); **Udo Hahn**, Nentershausen (DE); **Derek Allan Prater**, Cambridge (GB)

(73) Assignee: **Euro-Celtique S.A.**, Luxembourg (LU)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No : **08/677,798**

(22) Filed: **Jul. 10, 1996**

Related U.S. Application Data

(62) Division of application No. 08/241,129, filed on May 10, 1994, now Pat. No. 5,591,452.

(30) **Foreign Application Priority Data**

May 10, 1993	(DE)	43 15 525
Nov. 23. 1993	(GB)	9324045
Mar. 9, 1994	(GB)	9404544
Mar. 14, 1994	(GB)	9404928

(51) **Int. Cl.**[7] **A61K 9/22**

(52) **U.S. Cl.** **424/468**; 424/470; 424/476; 424/480; 424/488; 424/494; 424/495; 424/498; 424/499; 424/502; 514/646

(58) **Field of Search** 424/468, 470, 424/476, 480, 488, 494, 495, 498, 499, 502; 514/646

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,738,303	3/1956	Blythe et al	167/82
3,065,143	11/1962	Christenson et al	167/82
3,652,589	3/1972	Flick et al	260/326.5 M
3,830,934	8/1974	Flick et al	424/330
3,845,770	11/1974	Theeuwes et al	128/260
3,950,508	4/1976	Mony et al	424/19
3,965,256	6/1976	Leslie	424/22
3,974,157	8/1976	Shetty et al	260/247.2 B
4,013,784	3/1977	Speiser	424/19
4,063,064	12/1977	Saunders et al.	219/121
4,076,798	2/1978	Casey et al	424/22
4,088,864	5/1978	Theeuwes et al	219/121
4,132,753	1/1979	Blichare et al	264/25
4,259,314	3/1981	Lowey	424/19

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

2131350	3/1995	(CA)	A61K/31/135
3602370	8/1987	(DE)	A61K/45/06
3623193	1/1988	(DE)	A61K/31/205
4329794	3/1995	(DE)	A61K/31/135
4329794 A1	3/1995	(DE)	A61K/31/135
0032004	12/1980	(EP)	A61K/9/22
0043254	1/1982	(EP)	A61K/9/26
0097523	8/1983	(EP)	A61K/9/26
0043254	5/1984	(EP)	A61K/9/26
0108218	5/1984	(EP)	A61K/9/22
0108218 A2	5/1984	(EP)	A61K/9/22
0147780	12/1984	(EP)	A61K/9/32
0147780	7/1985	(EP)	A61K/9/32
0152379	8/1985	(EP)	A61K/9/50

(List continued on next page.)

OTHER PUBLICATIONS

Martindale, The Extra Pharmacopoeia, 28th Ed., 1982, 6263–c, Tramadol hydrochloride, pp 1029–1030.

Anderson, H.O. & Christensen, H., *In vitro and in vivo investigations of a new timed–release dosage form of propoxyphene hydrochloride,* Dansk tidsskrift for farmaci, vol. 43, 1969, pp 117–126.

Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14–Alkoxymorphinans,* Helvetica Chimica Acta, vol 72, 1989, pp 1233–1239.

Schmidhamer, Helmut, *Synthesis, Structure Elucidation, and Pharmacological Evaluation of 5–Methyl–oxymorphone,* Hevetica Chimica Acta, vol 71, (1988) pp 1801–1804.

Schmidhammer, Helmut, *Synthesis and Biological Evaluation of 14–Alkoxymorphinans,* J. Med Chem, (1990) vol 33. No. 4 , pp1200–1206.

ROTE LISTE® Service GmbH, Rote Liste 1998, Section 05.

Stanislaw Janicki and Zdzisiaw Jedras, *Slow–Release Microballs: Method of Preparation,* Acta. Pharm Technol 33(3) (1987), pp. 154–155.

B. Elsing and G. Blaschke, *Achiral and chiral high–performance liquid chromatographic determination of tramadol and its major metabolites in urine after oral administration of racemic tramadol,* Journal of Chromatography, 612 (1993), pp. 223–230.

C.H.W. Koks, A.P.E. Vielvoye–Kerkmeer, and J.H. Beijnen, *Tramadol (Tramal),* Pharm Weekbl 1993; 128(4): 1298–1300.

W. Lintz and H. Uragg, *Quantitative Determination of Tramadol in Human Serum by Gas Chromatography—Mass Spectrometry,* Journal of Chromatography, 341 (1985), pp 65–79.

(List continued on next page.)

Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

33 Claims, 1 Drawing Sheet

U S PATENT DOCUMENTS

4,343,789	8/1982	Kawata et al	424/78
4,366,172	12/1982	Lednicer	424/330
4,380,534	4/1983	Fukui et al	424/38
4,389,393	6/1983	Schor et al	424/19
4,421,736	12/1983	Walters	424/19
4,483,847	11/1984	Augart	424/22
4,533,562	8/1985	Ikegami et al	427/3
4,613,619	9/1986	Sleigh et al	514/546
4,708,874	11/1987	DeHaan et al	424/470
4,797,410	1/1989	El-Fakahany	514/356
4,801,458	1/1989	Hidaka et al	424/443
4,801,460	1/1989	Goertz et al	424/465
4,828,836	5/1989	Elger et al	424/419
4,834,984 *	5/1989	Goldie et al	424/488
4,834,985	5/1989	Elger et al	424/488
4,844,907	7/1989	Elger et al	424/465
4,844,909	7/1989	Goldie et al	424/480
4,861,598	8/1989	Oshlack	424/468
4,880,830	11/1989	Rhodes	424/470
4,894,234	1/1990	Sharma et al	424/440
4,917,899	4/1990	Geoghegan et al	424/461
4,925,675	5/1990	Giannini et al	424/469
4,935,246	6/1990	Ahrens	424/490
4,987,136	1/1991	Kreek et al	514/282
4,990,341	2/1991	Goldie et al	424/484
5,007,790	4/1991	Shell	424/451
5,023,089	6/1991	Sakumoto et al	424/502
5,026,560	6/1991	Makino et al	424/494
5,030,400	7/1991	Danielson et al	264/101
5,071,646	12/1991	Malkowaka et al	424/497
5,073,379	12/1991	Klimesch et al	424/467
5,126,145	6/1992	Evenstad et al	424/465
5,132,142	7/1992	Jones et al	427/196
5,133,974	7/1992	Paradissis et al	424/480
5,162,117	11/1992	Stupak et al	424/475
5,167,964	12/1992	Muhammad et al	424/482
5,169,645	12/1992	Shukla et al	424/499
5,178,868	1/1993	Mamqvist-Granlund et al	424/490
5,196,203	3/1993	Boehm	424/469
5,202,128	4/1993	Morella et al	424/469
5,204,119	4/1993	Shiobara et al	424/489
5,266,331	11/1993	Oshlack et al	424/468
5,271,934	12/1993	Goldberg et al	424/401
5,273,760	12/1993	Oshlack et al	424/480
5,286,493	2/1994	Oshlack et al	424/468
5,292,461	3/1994	Juch et al	264/37
5,300,300	4/1994	Egidio et al	424/456
5,321,012	6/1994	Mayer et al	514/25
5,330,766	7/1994	Morella et al	424/490
5,395,626	3/1995	Kotwal et al	424/472
5,403,593	4/1995	Royce	424/489
5,453,283	9/1995	Münch et al	424/489
5,468,744 *	11/1995	Raffa et al	514/282
5,472,710	12/1995	Klekkers-Bethke et al	424/468
5,521,178	5/1996	Nickel et al	514/23.2
5,549,912	8/1996	Oshlack	424/468

FOREIGN PATENT DOCUMENTS

0214735	7/1986	(EP)	A61K/9/22
0189861	8/1986	(EP)	A61K/47/00
0248548	5/1987	(EP)	A61K/9/22
0249347	5/1987	(EP)	A61K/31/485
0251459	5/1987	(EP)	A61K/9/22
0253104	6/1987	(EP)	A61K/9/00
0254978	2/1988	(EP)	A61K/9/22
0256127	2/1988	(EP)	C12N/9/00
0256127 B1	2/1988	(EP)	C12N/9/00
0267702	5/1988	(EP)	A61K/9/14
0271193	6/1988	(EP)	A61K/31/485
0271193 A2	6/1988	(EP)	A61K/31/485
0300897	7/1988	(EP)	A61K/9/22
0295212	12/1988	(EP)	A61K/47/00
0327295	8/1989	(EP)	A61K/9/52
0338383	10/1989	(EP)	A61K/9/54
0068450	1/1990	(EP)	A61K/9/20
0351580	1/1990	(EP)	A61K/9/22
0377518	1/1990	(EP)	A61K/9/52
0361680	4/1990	(EP)	A61K/9/46
0361910	4/1990	(EP)	A61K/9/16
0368247	5/1990	(EP)	A61K/9/26
0377517	7/1990	(EP)	A61K/31/52
0377518	7/1990	(EP)	
0298355	11/1990	(EP)	A61K/9/50
0415693	3/1991	(EP)	A61K/37/02
0430287 B1	6/1991	(EP)	A61K/9/54
0463833	6/1991	(EP)	A61K/9/26
0241615	9/1991	(EP)	A61K/9/22
0452145	10/1991	(EP)	A61K/9/14
0531611	4/1992	(EP)	A61K/9/02
0535841	9/1992	(EP)	A61K/31/485
0526862	2/1993	(EP)	A61K/9/20
0533297	3/1993	(EP)	A61K/9/16
0534628	3/1993	(EP)	A61K/31/485
0546676	6/1993	(EP)	A61K/31/60
0595311	5/1994	(EP)	A61K/31/44
0361910	6/1994	(EP)	A61K/9/16
0636370	2/1995	(EP)	A61K/31/485
0642788	3/1995	(EP)	A61K/31/135
0609961	8/1995	(EP)	A61K/31/485
0205282	9/1995	(EP)	A61K/9/22
0624366	5/1996	(EP)	A61K/31/135
2642420	3/1990	(FR)	C07C/55/10
997399	4/1964	(GB)	
1405088	6/1971	(GB)	A61K/9/26
1513166	6/1978	(GB)	B29B/1/02
2111386	12/1982	(GB)	A61K/9/20
2117239	3/1983	(GB)	A61K/9/20
2053681	4/1984	(GB)	A61K/9/22
2196848	5/1988	(GB)	A61K/9/22
2246514	2/1992	(GB)	A61K/9/16
2287880	10/1995	(GB)	A61K/9/14
54-92631	7/1979	(JP)	
4217925	8/1992	(JP)	
2568202	12/1996	(JP)	A61K/31/485
WO9119484	12/1991	(WO)	A61K/9/16
WO9119485	12/1991	(WO)	A61K/9/16
WO9201446	2/1992	(WO)	A61K/9/50
WO9202209	2/1992	(WO)	A61K/9/22
WO9205774	4/1992	(WO)	A61K/9/18
WO9206679	4/1992	(WO)	A61K/9/16
WO9300076	1/1993	(WO)	A61K/9/51
WO9304675	3/1993	(WO)	A61K/31/16
WO9307859	4/1993	(WO)	A61K/9/16
WO9307861	4/1993	(WO)	A61K/9/50
WO9317667	9/1993	(WO)	A61K/9/16
WO9318753	9/1993	(WO)	A61K/9/16
WO9324110	12/1993	(WO)	A61K/9/20
WO9403160	2/1994	(WO)	A61K/9/32
WO9403161	2/1994	(WO)	A61K/9/52
WO9405262	3/1994	(WO)	A61K/9/16
WO9422431	10/1994	(WO)	A61K/9/20
WO9423700	10/1994	(WO)	A61K/9/16
WO9514460	6/1995	(WO)	A61K/9/14

OTHER PUBLICATIONS

Pharm Res 1992; Supp 9:308, *Tramadol*, PPDM's 8207 and 8206

W. Lintz, H. Barth, G. Osterloh, and E. Schmid–Bothelt, *Bioavailability of Enteral Tramadol Formulations 1st Communication: Capsules,* Arzeimittel–Forschung. Drug Res 36 (II) Nr 8 (1986), pp 1278–1283.

Jean–Marie Besson and Michael D. Vickers, *Tramadol Analgesia Synergy in Research and Therapy,* Drugs 47 (Suppl. 1):1–2, 1994, Adis International Limited.

Pierre Dayer, Laurence Collart and Jules Desmeules, *The Pharmacology of Tramadol,* Drugs 47 (Suppl 1):3–7, 1994, Adis International Limited.

Abraham Sunshine, *New Clinical Experience with Tramadol,* Drugs 47 (Supp. 1) 8–18, 1994, Adis International Limited.

Klaus A. Lehmann, *Tramadol for the Management of Acute Pain,* Drugs 47 (Supp 1):19–32. 1994, Adis International Limited.

Keith Budd, *Chronic Pain—Challenge and Response,* Drugs 47 (Suppl. 1):39–43, 1994, Adis International Limited

Jordi Cami, Xavier Lamas and Magi Farre, *Acute Effects of Tramadol in Methadone–Maintained Volunteers,* Drugs 47 (Supp. 1):39–43, 1994, Adis International Limited

C. Rhoda Lee, Donna Mc Tavish and Eugene M. Surkin, "Tramadol, A Preliminary Review of its Pharmacodynamic Properties, and Therapeutic Potential in Acute and Chronic Pain States", Drugs 46(2):313–340, 1993, Adis International Limited.

Valerie Kayser, Jean–Marie Beeson, and Gisele Gilbaud, *Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat,* European Journal of Pharmacology, 224 (1992), pp. 83–88.

Kenzie L. Preston, Donald R. Jasinksi and Margaret Testa, *Abuse potential and pharmacological comparison of tramadol and morphine,* Drug and Alcohol Dependence, 27 (1991), pp. 7–17.

Valerie Kayser, Jean–Marie Beeson and Gisele Guilbaud, *Effects of the analgesic agent tramadol in normal and arthritic rats: comparison with the effects of different opioids, including and cross–tolerance to morphine,* European Journal of Pharmacology, 195 (1991) 37–45.

T. Murano, H. Yamamoto, N. Endo, Y. Kudo, N. Okada, Y. Masuda, and I. Yano, *Studies of Dependence on Tramadol in Rats,* Arzneimittel–Forschung, Drug Res 28(I) Heft 1a (1978).

T. Yanagita, *Drug Dependence Potential of 1–(m–Methoxyphenil)–2–(dimethylaminomethyl)–cyclohesan–1–ol Hydrochloride (Tramadol) Tested in Monkeys,* Arzneimittel–Forschung Drug Res 28(I), Heft 1a (1978), pp 158–163.

Abraham Sunshine, MD, Nancy Z. Olson, MPS, Itic Zighelboim, MD, Ana DeCastro, RN, and Frederick L. Minn, MD, PhD, *Analgesic oral efficacy of tramadol hydrochloride in postoperative pain,* Clin. Pharmacol Ter. (Jun. 1992), pp 740–146

Translation of Japanese Patent Publication No. 43 (1968) 20006, Detailed Description of the Invention

M. Ahmend and R P. Enever, *Formulation and Evaluation of Sustained Release Paracetamol Tablets,* Journal of Clinical and Hospital Pharmacy (1981) 6, pp. 27–38

M D. Vickers, D. O'Flaherty, S M. Szekely, M. Read and J. Yoshizumi, *Tramadol: pain relief by an opioid without depression of respiration,* Anaesthesia, 1992, vol. 47, pp. 291–296.

G M. Hanna, C A. Lau–Cam and W M. Plank, *Direct determination of the enantiomeric purity of tramadol hydrochloride by proton nuclear resonance (1H NMR spectroscopy with chiral lanthanide shifr reacgent,* Pharmazie 44 (1989). H 5, pp. 321–325

S J. Carter and R. Woodford, "Long–Acting Oral Medicaments", Pharmacy Digest (1961) pp. 183–189.

Remington's Pharmaceutical Sciences, 1980, p. 1598.

Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization II. Hydrophobic Substances as Meltable Binders,* Drug Development and Industrial Pharmacy, vol. 20, No. 7, (1984), pp. 1179–1197.

Von K. Flick, E. Frankus and E. Friderichs—Tramadol, 107–113, *Untersuchungen zur chemischen Strukkur und analgeslachen Wirkung von phenylsubstituterien Aminomethylgycolohexanglen,* Arzneimittel–Forschung, Drug Res. 28 (1), Heft 1a, and English translation.

Kuschinsky et al., *Kurges Lehrbuch der Pharmakologie und Toxikologie,* Georg Theimo Verlag Stuttgart, New York 1987, p270–273.

Von E. Frankus, H. Friderichs, S M. Kin und G. Osterloh, *Uber die Isomerentronnung, Strukuraufklarung und pharmakologische Charaklerisierung von 1–(m–Methoxyphenyl)–2–(dimethylaminomethyl)–cyclohexand–1–ol,* Arzneim–Forsch, Drug Res (I), Heft 1a (1978), 144–121 and English translation

Rote Liste 1992, Entry No. 05020

Derwent WPI C92–138727 Abstract JP 04/217 925 of 07 08 92.

Herbert P. Fiedler: Loxicon der Hilfastoffe, 34d Ed., 1989, p272–273.

Sueker et al., (Eds.), Pharmazeutische Technologie, Stuttgart 1979, p497–498.

Von W. Vogel, H. Burchardi, K. Sihler und L. Valic, *Über die Wirkung von Tramadol auf Almung und Kreislauf,* Arzneimittel–Forschung, Drug Res. 28(I), Heft 1a (1978), pp 183–186 and English translation.

Von W. Lintz, S. Erlacin, E. Frankus and H. Uragg, *Metabolismus von Tramadol bol Mensch and Tier,* Arzneimittel–Forschung, Drug Res 31 (II), Nr. 11 (1981), pp. 1932–1943 and English translation.

Von F. Lagler, F. Helm, V. Etzol und H. Kiel, *Toxikologisache Untersuchungen mit Tramadol einem neuen Analgelikum,* Arzneimittel–Forschung, Drug Res. 28(I), Heft 1a (1978), pp. 164–172 and English translation

Von G. Osterloh, E. Friderichs*, F. Felgenheuer*, W.A. Gunzler, Z. Henmi**, T. Kitano**, M. Nakamura**, H. Hayashi** und I. Ishii**, *Allgemeine pharmakologische Unternuchungen mit Tramadol einem stark wirkenden Analgenikum,* Arzneimittel–Forschung, Drug Res. 28(I). Heft 1a (1978) pp. 135–151 and Englisb translation.

Von E. Friderichs, F. Felgenhauer, P. Jongschaap und G. Osterloh, *Pharmakologische Untersuchungen zur Analgesic, Abhangigheim–und Toleranzentwicklung–von Tramadol. einem stark wirkenden Analgetikum,* Arzneimittel–Forschung Drug Res. 28(I), Heft 1a, pp. 122–134 and English translation.

L. Collart, C. Luthy, C. Favario–Constantin, P. Dayer, *Dualite de l'effel analgesique du tramadol chez l'homme,* Schwiz. Med. Wochenschr. 1993; 123: pp. 2241–2243 and English translation.

E. Beubler, *Medikamenlose Schmerzhergnie. Krieterien, Müglichkelten, Risken,* Therapiewoche Österreich 7,2 (1992), pp. 90–96 and English translation

Kaiko, et al., *A Single-dose Study of the Effect of Food Ingestion and Timing of Dose Administration on the Pharmacokinetic Profile of 30mg* Sustained-release Morphine Sulfate Tablets, Current Therapeutic Research, pp. 869–878, vol. 47, No. 5, May 1990.

Kaiko, et al., *Controlled-release Morphine Bioavailability (MS Contin™ Tablets) in the Presence and Absence of Food,* The Hospice Journal, pp. 17–30, vol. 6(4) 1990.

Gourlay, et al., *The Reproducibility of Bioavailability of Oral Morphine from Solution under Fed and Fasted Conditions,* Journal of Pain and Symptom Management, vol. 6, No. 7, Oct. 1991, pp. 431–436.

Gourlay, et al., *Influence of a High-fat Meal on the Absorption of Morphine from Oral Solutions,* Clin. Pharmacol. Ther., Oct. 1989, pp. 403–468.

Physicians Desk Reference 1994, 48th Edition, pp. 1821–1824.

Advertisement: Roxanol SR, 1988 Roxane Labs, Inc.

R. Kaiko and T. Hunt, *Comparison of the Pharmacokineric Profiles of Two Oral Controlled-Release Morphine Formulations in Healthy Young Adults,* Clin. Thera., vol. 13, No. 4, 1991, pp. 484–488.

Thomsen, L. Juul, *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, Part IV. Drug Content, Drug Particle Size, and Binder Composition,* Pharmaceutical Technology Europa (Oct. 1994), pp. 19–22.

McTaggart, C.M., et al., *The Evaluation of Formulation and Processing Conditions of a Melt Granulation Process,* Int. J. Pharm., vol. 19, No. 2, issued 198, pp. 139–148.

El-Shanawany, S., *Sustained Release of Nitrofurantoin From Inert Wax Matrixes,* J. Controlled Release, vol. 26, No. 1, issued 1993, pp. 11–19.

S. Bloomfield, et al., *Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations,* Clin. Pharmacol. Ther., vol. 53, No. 4, 1993, pp. 469–478.

Advertisement MS Contin™ 1986, 1987 The Purdue Frederick Company.

P. Flanders, et al., *The Control of Drug Releases From Conventional Melt Granulation Matrices,* Drug Development and Industrial Pharmacy, vol. 13, No. 6, (1987), pp. 1001–1022.

T. Schaefer, et al., *Melt granulation in a laboratory scale high shear mixer,* Drug Development and Industrial Pharmacy, vol. 16, No. 8, (1990), pp. 1249–1277.

Thompson, L. Juul et al., Schaefer, T., et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, I. Process Variables,* Drug Development and Industrial Pharmacy, vol. 19, No. 15, pp. 1867–1887.

Thomsen, L. Juul, et al., *Prolonged Release Matrix Pellets Prepared by Melt Pelletization, Part IV, Drug Content, Drug Particle Size, and Binder Composition,* Pharmaceutical Technology Europe, (Oct. 1994), pp. 19–24.

Thomsen, L. Juul, *Utilizing melt pelletization technique for the preparation of prolonged release products, Pelletization,* (material elaborated by Assistant Prof. Lars Juul Thomsen, Dept. of Pharmaceutics, Royal Danish School of Pharmacy for the DIE course "Pelletization Technology", Nov. 1992, Sections I to VI.

SK Baveja et al., Int. J. Pharmaceutics, 41, (1988) p55–62.

Formulating for Controlled Release with METHOCEL® Premium Cellulose Ethers. The Dow Chemical Company, 1989.

M.S. Vasquez et al., Drug Dev. & Ind. Pharmacy, 18 (11 & 12), p1355–1378 (1992).

L.W.S. Cheong et al, Pharm. Res. 9(11) p1510–151 (1992).

Pharmazeutische Stoffiste 6th Ed., 1985 p. 196.

Rote Liste 1993 Nos. 05001 & 05008.

Derwent Abstract 92:64751 1985.

Haltbarkeim-Herstellungsdalen deutscher Arzneimittel p486 1985.

Goodman and Gilmans, 8th Ed., 1990:p497.

Hunt, et al., Clin. Ther. vol. 13, No. 4, 1991, pp. 482–488.

Lee et al. Drugs 46(2), 1993, pp. 313–340.

The Merck Index 11th Ed., 1989.

Pharmazeulische Stoffiate 10, Auflage, p. 193, 11/94.

Rote Liste 1992 Entry 05007.

PIL (Product Information Leaflet) about MST CONTINUS® tablets.

Graph of dissolution rates claimed in the patent EP 0 624 366.

The Physician's Desk Reference, 1994 Monograph on MS CONTIN® (MST CONTINUS®) tablets.

DA Aldermann, Int. J. Pharm. Tech. and Prod. Mfr., 5(3) p1–9, 1984.

HE Huber et al., J. Pharm. Sci. 55 (9) Sep. 1966, p974–976.

Lin SY et al., Current Therapeutic Research 52 (3), p. 486–492, Sep., 1992.

Handbook of Pharmaceutical Excipients, p138–140, 1986.

Aqualon Technical Information Bulletin VC-585, 1991.

P Colombo, Advanced Drug Delivery Reviews, 11 (1993) p37–57.

KV Ranga Rao et al., Int. J. Pharmaceutics, 48 (1988) p1–13.

JE Hogan, Drug Dev. & Ind. Pharmacy, 15 (6 & 7), p975–999 (1989).

JL Ford et al., Int. J. Pharmaceutics, 24 (1985) p327–338.

PB Daly et al. Int. J. Pharmaceutics, 18 (1984) p201–205.

H. Lapidus et al., J. Pharm. Sci., 55(8), Aug. 1966, p840–843.

H. Lapidus et al., J. Pharm. Sci., 57(8), Aug. 1968, p1292–1301.

Abstract of JP 54/092631, published Jul. 23, 1979.

J.M. Aiache and J. Hirtz, *Biopharmaceutics—Absolute Bioavailability of Tramal Suppositories,* Third European Congress of Biopharmaceutics and Pharmacokinetics Proceedings—vol. 1, p. 311, 1992.

Clinical Pharm. & Ther. vol. 53, No. 2, *American Society for Clinical Pharmacology and Therapeutics,* P111–67, P111–68 and P111–69, 1993.

* cited by examiner

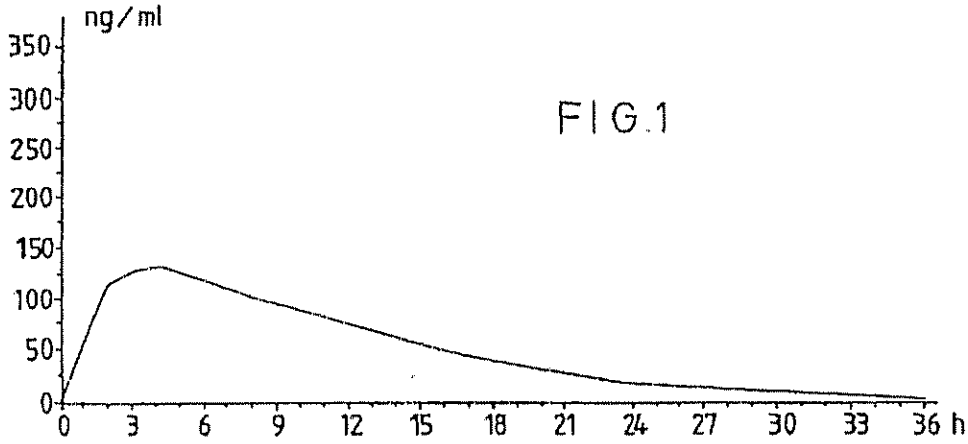
ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

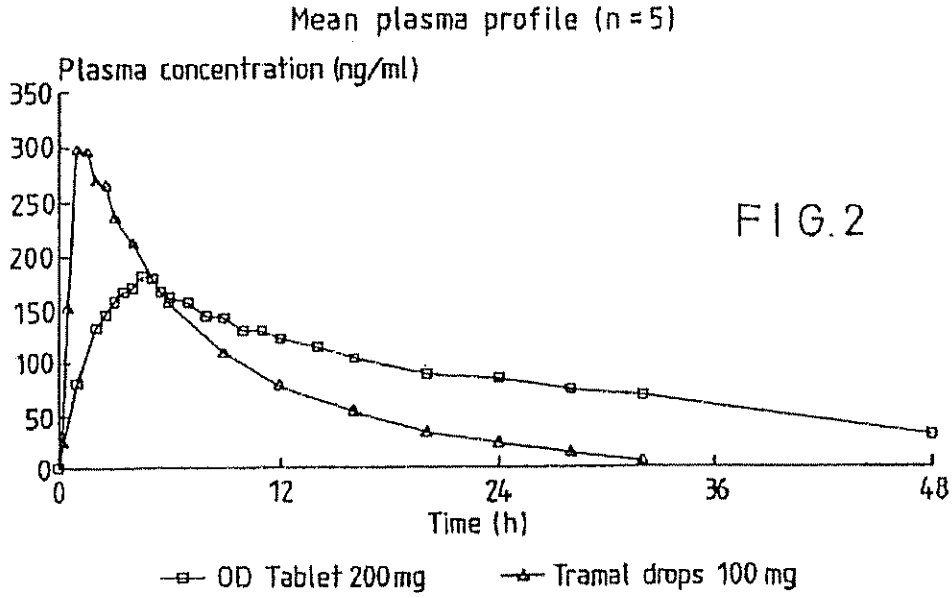
Mean plasma profile (n = 5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200 mg
Tramal drops 100 mg

FIG.2

CONTROLLED RELEASE TRAMADOL

This is a divisional of application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452)

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (+)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75

TABLE 2-continued

TIME (H)	% RELEASED
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate if tramadol released

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm.

The in vitro absorption rate is determined from measurement of plasma concentration against time using the deconvolution technique. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include:

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethylacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert nonpareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent

(d) optionally repeating steps (c) and possibly (b) one or more times

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued.

It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy

Energy may also be delivered through oiler means such as by a heating jacket or via the mixer impeller and chopper blades

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed onNov. 23, 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica. Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

BRIEF DESCRIPTION OF DRAWINGS

The present invention is further illustrated in connection with the accompanying drawings in which:

FIG. 1 is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers: and

FIG. 2 is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation wee prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68 0
Ethylcellulose (Surelease @ 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur (Dehydag wax 0)	42 00
Magnesium Stearate Ph. Eur	2 00
Purified Talc Ph. Eur	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1 6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below

	mg/tablet
Hydropopylmethylcellulose Ph. Eur 15 cpu (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3 87
Opaspray M-1-7113B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0 270
Purified Water Ph. Eur	55 52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100 0
Lactose Ph. Eur.	58 0
Ethylcellulose USNF	15 0

-continued

	mg/tablet
(Ethocel 45 CP)	
Cetostearyl alcohol Ph. Eur	52.0
(Dehydag wax O)	
Magnesium stearate Ph. Eur	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur	2.00
Purified talc Ph. Eur	3.00

In vitro dissolution studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. 1.

EXAMPLES 4 AND 5

Particles having the formulations given in Table II below were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a 10 liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph Eur. Paddle Method 100 rpm, 0.1 N HCl

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol Hcl	200	360	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7 63	11.44	15 25
Magnesium Stearate	5 16	7 63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved

EXAMPLE 8

Example 4 was repeated but with (lie following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7 66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mmx6 5 mm normal concave capsule shaped plain/plain punches

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50

-continued

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG 2 in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1 A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hours after oral administration.

2. A controlled release preparation as claimed in claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. And using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

3. A controlled release preparation as claimed as claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0 1 N hydrochloric acid at 37° C and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

4. A controlled release preparation as claimed in claim 1, having an in vitro dissolution rate (measured by the Ph Eur

Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–30
2	0–45
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80.

5. A controlled release preparation according to claim 1, wherein said substrate comprises a plurality of spheroids.

6. A controlled release preparation according to claim 5, wherein said spheroids comprise a spheronizing agent

7. A controlled release preparation suitable for dosing every twelve hours comprising

a substrate comprising an effective amount of tramadol or pharmaceutically acceptable salt thereof and said substrate coated wit a controlled release coating;

said preparation exhibiting an in vitro dissolution rate when measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm, such that between 5 and 50% (by weight) tramadol is released after 1 hour, between 10 and 75% by weight) tramadol is released after 2 hours, between 20 and 95% (by weight) tramadol is released after 4 hours, between 40 and 100% (by weight) tramadol is released after 8 hours, more than 50% (by weight) tramadol is released after 12 hours, more than 70% (by weight) tramadol is released after 18 hours and more than 80% (by weight) tramadol is released after 24 hours said preparation providing a therapeutic effect for at least about 12 hours after oral administration.

8. A controlled release preparation according to claim 7, wherein said substrate comprises a plurality of spheroids

9. A controlled release preparation according to claim 7 which provides a t_{max} at 2 to 7 hours after oral administration.

10. A controlled release preparation according to claim 7, which provides a t_{max} at 1.5 to 8 hours after oral administration.

11. A controlled release preparation according to claim 7, which provides a W_{50} from about 7 to about 16 hours after oral administration

12. A controlled release preparation according to claim 7, wherein said substrate is a tablet

13. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, and providing a W_{50} in the range of 10 to 33 hours when orally administered.

said coated tablet providing a therapeutic effect for about 24 hours after oral administration

14. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet providing a therapeutic effect for about 24 hours after oral administration and having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

15. A controlled release oral pharmaceutical tablet in accordance with claim 15 which has

an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. using UV detection at 27 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

16. A controlled release preparation according to claim 1, which when orally administered provides a W_{50} value in the range of 10 to 33 hours.

17. A controlled release preparation according to claim 1, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75.

18. A controlled release preparation according to claim 1, which when orally administered provides a t_{max} at 4–5 hours after oral administration.

19. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of an opioid analgesic consisting essentially of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hour, after oral administration.

20. A controlled release preparation according to claim **1**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

21. A controlled release preparation according to claim **7**, wherein said substrate comprises inert nonpareil beads coated with said tramadol.

22. A controlled release preparation according to claim **19**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

23. A controlled release preparation according to claim **19**, wherein said substrate is a tablet.

24. A controlled release preparation according to claim **19**, wherein said substrate comprises spheroids.

25. A controlled release preparation according to claim **19**, which provides a t_{max} from 3 to 6 hours after orally administered to a human patient.

26. A controlled release preparation according to claim **25**, which provides a W_{50} value in the range from 10 to 33 hours.

27. A controlled release preparation in accordance with claim **1**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

28. A controlled release preparation in accordance with claim **7**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

29. A controlled release preparation in accordance with claim **13**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

30. A controlled release preparation in accordance with claim **14**, wherein said controlled release coating comprises a material selected tom the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

31. A controlled release preparation in accordance with claim **19**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

32. A controlled release preparation in accordance with claim **26**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

33. A controlled release preparation in accordance with claim **11**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

* * * * *

EXHIBIT F

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 4

Patent #: 6254887 **Issue Dt:** 07/03/2001 **Application #:** 08677798 **Filing Dt:** 07/10/1996

Inventors: RONALD B. MILLER, STEWART T. LESLIE, SANDRA T. A. MALKOWSKA, KEVIN J. SMITH et al

Title: CONTROLLED RELEASE TRAMADOL

Assignment: 1

Reel/Frame: 019317/0262 **Recorded:** 05/15/2007 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: MUNDIPHARMA GMBH **Exec Dt:** 05/03/2007

Assignees: NAPP PHARMACEUTICAL GROUP LIMITED
MILTON ROAD
CAMBRIDGE SCIENCE PARK
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PURDUE PHARMA PRODUCTS L.P.
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ONE STAMFORD FORUM
STAMFORD, CONNECTICUT 06901

Correspondent: DAVIDSON, DAVIDSON & KAPPEL, LLC
14TH FLOOR
485 SEVENTH AVENUE
NEW YORK, NY 10018

Assignment: 2

Reel/Frame: 019317/0258 **Recorded:** 05/15/2007 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)

Assignor: EURO-CELTIQUE S.A. **Exec Dt:** 05/04/2007

Assignees: NAPP PHARMACEUTICAL GROUP LIMITED
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PURDUE PHARMA PRODUCTS L.P.
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STAMFORD, CONNECTICUT 06901

Correspondent: DAVIDSON, DAVIDSON & KAPPEL, LLC
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485 SEVENTH AVENUE
NEW YORK, NY 10018

Assignment: 3

Reel/Frame: 019317/0266 **Recorded:** 05/15/2007 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: NAPP RESEARCH CENTRE LIMITED **Exec Dt:** 05/04/2007

Assignees: NAPP PHARMACEUTICAL GROUP LIMITED
MILTON ROAD

CAMBRIDGE SCIENCE PARK
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PURDUE PHARMA PRODUCTS L.P.
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Assignment: 4

Reel/Frame: 019317/0396 **Recorded:** 05/15/2007 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)

Assignor: MUNDIPHARMA AG (A.K.A. MUNDIPHARMA S.A.) **Exec Dt:** 05/04/2007

Assignees: NAPP PHARMACEUTICAL GROUP LIMITED
MILTON ROAD
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PURDUE PHARMA PRODUCTS L.P.
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NEW YORK, NEW YORK 10018

EXHIBIT G

REDACTED IN ITS ENTIRETY

EXHIBIT H

ATTACHMENT A

222.94213 DIV

UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Ronald B. MILLER, et al.
	Serial No.:	08/449,772
	Filed:	May 24, 1995
	For:	CONTROLLED RELEASE FORMULATION

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

July 17, 1997

Sir:

In accordance with 37 C.F.R. paragraphs 1.97-1.99, copies of the references listed on the attached form PTO-1449 are enclosed herewith.

The Examiner's attention is drawn to the fact that a corresponding European Patent EP 0 624 366 B1 has now been opposed by seven (7) opposers. The granted claims of EP 0 624 366 B1 are directed to compositions and are different than the pending claims in the present application. The corresponding Chilean Patent Application 667-94 has also been opposed by one of the opposers of the European patent. The documents cited in the Chilean Opposition have also been cited in the European Opposition.

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on July 22, 1997.

STEINBERG, RASKIN & DAVIDSON, P.C.

BY: [signature]

G:\CLIENTS\222\94213DIV\PROSECUTION\IDSJULY 21

In order to ensure compliance with disclosure requirements under Rule 56, Applicants submit herewith a PTO-1449 form which lists each and every reference which has been cited in the above-mentioned EP Opposition. In addition, submitted herewith are copies of the Opposition papers (or English translations thereof where appropriate) submitted by each opponent. These copies include submissions by Arzneimittelwerk Dresden GmbH, Bioglan Laboratories Ltd., Gruenenthal GmbH, Krewel Meuselbach GmbH, Hexal AG, Lannacher Heilmittel GmbH, and Nycomed Danmark A/S. For the Examiners convenience, Applicants have separately enclosed Appendix A, which correlates the references cited by the opposers. Certain of these references have already been cited by Applicants in a previous Information Disclosure Statement and have already been considered and made of record by the Examiner. However, for the sake of completeness, Applicants have once again provided copies of the previously cited documents.

The Examiner's particular attention is drawn to the fact that the U.S. Patent corresponding to EP 147 780, cited and relied upon by several opponents, has previously made of record in both the present application and in the parent application (U.S. Patent No. 5,591,452)

The Examiner's attention is also directed to the page 8 of the twelve page PTO-1449 form that was submitted with Applicants' Information Disclosure Statement of August 15, 1994. On that page, the Examiner indicated that certain references were not considered. Applicants have once again recited these references on the present PTO-1449 form, and have resubmitted copies of these references, along with English translations where appropriate.

Applicants have also obtained English translations of certain non-English language journal articles that were previously cited in the Information Disclosure Statement mailed October 20, 1995. Copies of both the journal articles and their English translations are submitted herewith for the Examiner's further consideration.

The undersigned also respectfully directs the Examiner's attention Assignee's co-pending patent applications U.S. Serial Nos. 08/774,229; 08/404,293; 08/607,852; 08/343,630; 08/607,851; and 08/843,571 Abandoned application 08/269,208 is also brought to the Examiner's attention.

It is respectfully requested that all of the references cited herein be made of record in the instant application. A check in the amount of $230.00 is enclosed to cover the cost of the fee for entering this Information Disclosure Statement.

Respectfully submitted,
STEINBERG, RASKIN & DAVIDSON, P.C.

By _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

EXHIBIT I

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 735113 (87145/98). In the name of: Mundipharma Medical GmbH

- and -

OPPOSITION THERETO BY: Grunenthal GmbH under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, **Kenneth Frederick Brown**, Consultant Pharmaceutical Scientist in Pharmaceutics of 209 Burraneer Road, Coomba, NSW, 2428, Australia, declare as follows:

1 BACKGROUND and QUALIFICATIONS

1.1 I am currently self employed (part-time) as a Consultant Pharmaceutical Scientist in Pharmaceutics. Pharmaceutics is the science of the design, formulation, development and evaluation, both *in vitro* and *in vivo* of pharmaceutical dosage forms.

1.2 I received the degrees of Bachelor of Pharmacy, Master of Pharmacy and Doctor of Philosophy in Pharmaceutics from the University of Sydney NSW 2006 in 1963, 1965 and 1968 respectively.

1.3 After the completion of my doctorate I spent one year as a postdoctoral fellow in the Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, NY, USA. Thereafter I returned to the

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Ref 205485059

Kenneth F Brown

Department of Pharmacy, University of Sydney as a Lecturer in Pharmaceutics (1969-1975) and Senior Lecturer (1976-1988).

1.4 During 1975-1976 I was a Visiting Lecturer at the School of Pharmacy, University of Manchester, UK for one year. In 1985 I spent six months as a Visiting Scientist at the Departement de Pharmacologie, Faculte de Medecine de Creteil, Universite de Paris XII, Paris. During that period I visited Schools of Pharmacy and presented invited research seminars at Marseilles, Leeuwin, Utrecht, Brighton, Bath and Cardiff as well as in Creteil where I was based. The seminars covered a wide range of my research results including the areas of physical pharmaceutics and biopharmaceutics. I also presented pharmacokinetics research at the 1985 British Pharmaceutical Conference in Leeds.

1.5 In February 1988 I left the University of Sydney to become Medical and Technical Director of 3M Riker (later renamed 3M Pharmaceuticals), a division of 3M Healthcare Australia at Chilvers Road, Pennant Hills, New South Wales. In that position I was responsible for all research and development and technical affairs of the division, including clinical research, regulatory affairs, medical services, laboratory product development and quality assurance for new and marketed products for the region including Australia, New Zealand and Asia (excluding Japan).

1.6 During the time of my employment there, 3M Pharmaceuticals was extensively involved in development of controlled release preparations including 12-hour and 24-hour oral controlled release capsules of theophylline and transdermal patches for coronary vasodilatation and hormone replacement therapy among others. I participated directly in clinical trials for several of those products and supervised staff conducting trials in a number of others. As Medical Director it was my responsibility to select and visit the investigators, inspect the facilities develop and approve the budget and the protocol including trial design, analytical methodology, data treatment and patient inclusion criteria. The day to day management of case records was the responsibility of the investigator and a dedicated clinical research officer under my supervision. In trial design and data management there were usually intensive discussions with and assistance from 3M global laboratory staff to arrive at optimum protocol end points. I believe this is typical of the procedure used in most multinational pharmaceutical companies. For products which we developed locally in the 3M Australia R and D

Kenneth J Brown

laboratories the clinical trials were performed entirely locally, by specialist investigators, occasionally with the assistance of consultants.

1.7 As regional manager for research and development I represented the Australian subsidiary of 3M Pharmaceuticals at the global research management meetings. This group was responsible for review and evaluation of data and progress of all projects undertaken by 3M Pharmaceuticals worldwide. In Australia, I was responsible for the management of four subsidiary departments and a staff, which at the time of my resignation in 1992, numbered 27.

1.8 In September 1992, I rejoined the Department of Pharmacy (since 1 January 2000 the Faculty of Pharmacy in the College of Health Sciences), University of Sydney as Professor of Pharmaceutics. At that time, to my knowledge, there were four Professors of Pharmaceutics in Australia. I remained in that position until my retirement in April 2000. The Pharmaceutics group at the University comprised one Professor, 4 Senior Lecturers and 3 Lecturers. There were also several Associate Lecturers and at any particular time there were between 15 and 20 postgraduate candidates for MSc and PhD degrees.

1.9 Exhibited to me and marked with the letters "KFB-1" is a copy of my curriculum vitae. I have supervised the research projects of twelve PhD graduates and shared the supervision of a further five PhD students and numerous MSc graduates. I worked in very close cooperation with these students. To the best of my knowledge, nine of the above PhD students had completed their degrees before I joined the pharmaceutical industry in 1988 and a tenth was essentially complete. The nature of the research that we were conducting at that time can be judged from the titles of publications 1 to 44. Of course not all the research was published but the published work is typical. These research students were all enrolled as Pharmaceutics PhD students but the subjects of their research often involved collaboration with other disciplines. I have published about 67 papers almost all of which have appeared in international, peer reviewed journals and have given many presentations and abstracts at conferences.

1.10 My early research involved investigating the nature of interactions of drugs and other small molecules with macromolecules of synthetic and natural origin. This work principally involved physical pharmaceutics. My

Kenneth F Brown

experience in this research area is helpful in understanding polymeric materials and the nature and significance of intermolecular interactions in dosage form design.

1.11 I have also conducted research and have extensive experience in postgraduate teaching of practical and theoretical aspects of dissolution kinetics. This research and scholarship is most valuable in understanding the diffusional processes involved in the release and absorption of drugs from immediate release and controlled release dosage forms. Many of my publications describe biopharmaceutical studies of the determinants of distribution and disposition of drugs in the body and the influence of disease states and stress conditions on that disposition. Many of the studies make use of pharmacokinetic concepts for the interpretation of the experimental findings and significance. Eleven of my publications report direct investigations of pharmacokinetics and clinical pharmacokinetics. Those will be apparent from reading of my curriculum vitae (KFB-1).

1.12 Pharmaceutics, has been the focus of my academic and professional career. Since 1965 I have worked as an academic and in private industry and led or been part of research groups that have undertaken research in a range of areas including physical pharmacy, dosage form design and formulation, bioavailability, drug metabolism and pharmacokinetics.

1.13 Further, as a research scientist and the leader of an active research group, the Professor of Pharmaceutics at the University of Sydney and the Medical and Technical Director of 3M Pharmaceuticals, I was required to have and to maintain a strong working knowledge of the Australian and international scientific literature concerning pharmaceutical research and development.

1.14 I have been a long term member of a number of research societies, including the Australasian Pharmaceutical Science Association (of which I was President from 1992 to 1998) and The Australasian Society of Clinical and Experimental Pharmacologists. Details of the committees and Boards that I have been involved with over the years are provided in my curriculum vitae (KFB-1).

2 MY INSTRUCTIONS

2.1 I have previously been provided with a copy of a document entitled "*Guidelines for Expert Witnesses in Proceedings in the Federal Court of Australia*" and I am aware of my obligations as an expert in these proceedings.

2.2 MM's Patent Attorneys have also provided me with copies of the following documents:

2.2.1 The patent specification accompanying Australian Patent Application 735113 (AU-B-87145/98) in the name of MM, entitled "Opioid Formulations For Treating Pain" ("the Patent Specification");

2.2.2 The Statutory Declaration of Stephan A Schug that was executed on 22 June 2003 ("the Schug Declaration").

2.3 I have been asked to review the above documents and address a number of matters concerning the Patent Specification:

2.3.1 Whether "the maximum plasma concentration (C_{max}) being from about 2.6 to 3.4 times the plasma concentration at 24 hours (C_{24})" (as mentioned in claim 1 of the Patent Specification) is disclosed elsewhere in the Patent Specification;

2.3.2 comment on what information the Patent Specification contains in relation to the production of a formulation and its use as mentioned in claim 1 of the Patent Specification; and

2.3.3 comment on what the information in the Patent Specification informs me about the duration of effect of the formulations referred to as Example 1 and Example 3 in the Patent Specification.

I have done this and my comments are set out in this statutory declaration.

2.4 In this statutory declaration I refer to and discuss a number of documents. I am informed by the patent attorneys representing MM in these proceedings that a copy of each of the documents that I discuss in this declaration has already or will be separately filed and served in relation to this opposition.

3 THE PATENT SPECIFICATION

3.1 I am informed by the patent attorneys for MM that the Patent Specification claims an earliest priority date of 23 November 1993.

3.2 The Patent Specification describes a method of treating pain in human subjects by administration of a controlled release opioid formulation with 24 hour efficacy. Claim 1 in the Patent Specification reads:

> *A method of effectively treating pain in humans, comprising orally administering to a human patient on a once-a-day basis an oral sustained release opioid pharmaceutical composition comprising a plurality of inert pharmaceutical beads coated with an analgesically effective amount of an opioid analgesic, said opioid coated beads overcoated with an effective amount of at least one hydrophobic polymer selected from the group consisting of a pharmaceutically acceptable acrylic polymer, a hydrophobic cellulosic material, and combinations thereof, said pharmaceutical composition providing a time to maximum plasma concentration $T_{(max)}$from about 2 to 8 hours and a maximum plasma concentration $C_{(max)}$ which is from about 2.6 to 3.4 times the plasma level of said opioid in said patient at 24 hours after single administration of the dosage form.*

3.3 Claim 1 in the Patent Specification relates to a method of treating pain in a human subject using a controlled release opioid formulation that is effective when administered once a day. Claim 1 alone provides a substantial amount of information concerning the controlled release formulation in terms of:

(i) its physical structure *i.e.* it is designed for oral administration and incorporates inert pharmaceutical beads coated with opioid and then overcoated with a controlled release coating with particular constituents; and

(ii) its performance, *in vivo*, *i.e.* upon administration it releases its opioid in a way that enables once daily dosing and in a manner that results in a plasma concentration curve with a profile that reflects an effective amount of opioid 24 hours after administration, a $T_{(max)}$ from about 2 to 8 hours, a C_{max}/C_{24} ratio of about 2.6 to 3.4 after single administration.

3.4 Based on the data in the Patent Specification, the formulations, referred to as Example 1 and Example 3 in the Patent Specification, meet the requirements set out in claim 1 in terms of the structure and performance characteristics I mention above at paragraph 3.3. Furthermore, there is other information in the Patent Specification that would assist me to produce and test a range of controlled release formulations according to claim 1 and have them assessed *in vivo* in patient trials to assess their performance. I will discuss this in more detail in the next section of my declaration.

4 THE SCHUG DECLARATION

4.1 I have been asked to read the Schug Declaration and comment on the matters it raises concerning the ratio of C_{max}/C_{24} recited in the claims of the Patent Specification and what information the Patent Specification provides concerning the production of controlled release formulations for treating pain in human subjects when administered on a once a day basis according to claim 1 in the Patent Specification. I have done this and my comments are set out below.

C_{max}/C_{24}

4.2 In paragraph 18 of the Schug Declaration is a description of how the values of C_{max}/C_{24} referred to were calculated for MS Contin® and Examples 1, 2 and 3 using the plasma concentration – time data in Table 6 and Table 13 of the Patent Specification. Table 6 contains mean (±SD) plasma concentration-time data obtained by averaging the plasma concentrations obtained in ten individual males who participated in the single dose, four-way crossover pharmacokinetic/pharmacodynamic trial described on page 30 to 32 of the Patent Specification. Similarly Table 13 contains mean (±SD) plasma concentration-time data obtained from averaging the data of thirteen individual males who participated in the single dose three-way crossover trial described on page 42 of the Patent Specification. Each individual subject of each trial had blood sampled at the twenty four hour time point, thus the mean values of C_{24} calculated from the ten subjects of Table 6 and the thirteen subjects of Table 13 respectively are true mean values. However, C_{max} values are not determined in the same way. Each of the ten individuals of the first trial and the thirteen individuals of the second trial would exhibit a unique C_{max} which depends on individual pharmacokinetic determinants including at

least gastrointestinal transit, rates of absorption, distribution and elimination.

4.3 The mean value of C_{max} is correctly obtained by determining the individual values of C_{max} and then determining the average. It is my understanding that such values of C_{max} for MS Contin® (fasted), Example 2 (fasted), Example 1 (fasted) and Example 1 (fed) are shown in Table 7 of the Patent Specification. These values differ significantly from those obtained by Professor Schug on page 5 of the Schug Declaration from observation of the group mean plasma concentrations.

4.4 Similarly mean values of C_{max} for the thirteen individuals who received MS Contin® (fasted) and Example 3 (fed) are, I believe, shown in Table 14 and are also significantly different from those obtained by Professor Schug on page 5 of the Schug Declaration. I have thus calculated values of C_{max}/C_{24} for Examples 1 and 3 respectively using the C_{max} values in Table 7 and Table 14 and the mean values of C_{24} from Table 6 and Table 13 respectively and these are set out in the table hereunder at paragraph 4.5.

4.5 The formulations referred to as Examples 1 and 3 in the Patent Specification have a physical structure in accordance with claim 1 [see pages 28-30 and 40-42]. These formulations were administered to human subjects for clinical evaluation and performed in accordance with claim 1 as follows:

Feature	**Example 1** **(values correct to one decimal point)**	**Example 3 (fed)** **(values correct to one decimal point)**
T_{max} 2-8 hours	5.9 and 6.9 hours [Table 7]	8.0 hours [Table 14]
C_{max}/C_{24}	3 and 3.4	2.6

Information in the Patent Specification concerning the production of controlled release formulations

4.6 At November 1993, the general approach to the design of controlled release formulations was to:

4.6.1 use information concerning the active agent such as dose, half-life, absorption etc and design and produce a range of formulations that would, theoretically, be expected to release the active agent at a rate and in a manner that would be suitable for use *in vivo*;

4.6.2 assess the formulations *in vitro* to ascertain whether the formulations reproducibly release the active ingredient appropriately for *in vivo* purposes; and

4.6.3 assess the formulations that pass the *in vitro* tests *in vivo* through the use of appropriately designed clinical trials.

4.7 The problem with the above process, that still exists today, is that although *in vitro* trials can be used as an initial screen they are not indicative of *in vivo* performance. Thus, the design of controlled release formulations generally involves the design and testing of multiple candidate formulations to arrive at a suitable formulation for use in human subjects.

4.8 I have been asked to comment on what controlled release opioid formulations, as referred to in claim 1 in the Patent Specification, I could have designed, produced and tested at November 1993 using the information in the Patent Specification and trials and experimentation that were routinely used by those in the controlled release formulation field at the time.

4.9 As I mentioned above, claim 1 provides information concerning the controlled release formulation administered to subjects on a once a day basis. In addition to the information in claim 1, other parts of the Patent Specification provide further information concerning the formulation as follows:

4.9.1 a range of opioids are described at line 20, page 11 to line 29 page 12;

Kimberly J. Brown

- 9 -

4.9.2 inert pharmaceutical beads are described at lines 11-14 on page 14;

4.9.3 hydrophobic overcoats that retard release of the active agent are described at line 24 page 14 to line 18 page 18;

4.9.4 approaches for modifying the release profile of a given formulation are described at: lines 24 page 14 to line 8 page 15; lines 19-29 on page 18; line 32 page 19 to line 8 page 20; line 34 page 20 to line 32 page 21; and line 15 page 25 to line 12 page 26.

4.10 With the above in mind at 23 November 1993, using the information in the Patent Specification, the following could have been completed without undue experimentation:

4.10.1 produce a range of opioid controlled release formulations that met the physical characteristics in claim 1 and included a controlled release coating that would have been expected to enable the formulations to meet the *in vivo* criteria in claim 1;

4.10.2 subject the candidate formulations to *in vitro* testing and select those that would have been likely to meet the *in vivo* criteria in claim 1; and

4.10.3 subject the candidate formulations selected from the previous step to *in vivo* testing to identify those that met the *in vivo* criteria (T_{max}, duration of effect and C_{max}/C_{24}) in claim 1.

4.11 Whilst the information in claim 1 of the Patent Specification is all that would have been required to carry out the above process at 1 July 1993, the information in the Patent Specification, concerning Examples 1 and 3, would also have assisted me in designing alternative formulations. Although both these formulations include an immediate release morphine component I could have used these formulations to design and test other formulations without an immediate release layer that would still meet the *in vivo* performance characteristics in claim 1.

4.12 Particular data concerning Examples 1 and 3 in the Patent Specification that would have been useful include the data from the clinical studies and

the *in vitro* data in Tables 3 and 10 that I could have used as a guide for assessing other formulations *in vitro*.

Duration of Effect

4.13 I have also been asked to review the clinical data concerning Examples 1 and 3 in the Patent Specification and comment on whether they are indicative of the formulations being suitable for administration on a once a day basis. I have done this and my comments are provided hereunder.

Examples 1 and 3

4.14 Examples 1 and 3 were tested in clinical studies using MS Contin®, a controlled release morphine preparation that I understand can be used to effectively treat pain when administered every 8-12 hours, as the reference formulation or comparator. The data generated are contained, in part, in Tables 4-7, 11-14 and Figures 9 and 10.

4.15 Using the data in Tables 6 and 13 I have estimated the following morphine plasma concentrations.

Morphine Formulation/time point	**Morphine Plasma Concentration (ng/ml)**	**Source of data**
MS Contin® at 12 hours	1.7 (fasted)	Table 6
Example 1 at 24 hours	1.7 (fed) 1.8 (fasted)	Table 6
MS Contin® at 12 hours	1.58 (fasted)	Table 13
Example 3 at 24 hours	2.1 (fed)	Table 13

4.16 The data in the above table show that the 24 hour morphine plasma levels in subjects receiving Example 1 or 3 were the same or higher than the 12 hour morphine plasma levels in subjects receiving MS Contin®. On the basis that MS Contin® is effective for up to 12 hours, I believe the data provide good evidence that the formulations of Example 1 and 3 have an extended therapeutic duration of effect of about 24 hours.

Kenneth J Brown

4.17 Furthermore, the data concerning Examples 1 and 3 are based on 30mg of morphine. If higher morphine plasma levels were desired using the formulations of Example 1 or 3 this could be achieved by increasing the dose of morphine in the formulation. I was unaware of the formulations of Examples 1 and 3 at 23 November 1993, but had I been aware and had access to the other information and data in the Patent Specification, preparing a controlled release formulation with an increased amount of morphine, relative to the formulation of Example 1 or 3, to achieve higher morphine plasma levels over a 24 hour period would have been a reasonably simple exercise.

AND I make this solemn declaration by virtue of the Statutory Declarations Act, 1959 and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DECLARED at: Sydney, New South Wales this 1st day of June 2005

KENNETH FREDERICK BROWN

BEFORE me:.....

Phillip Kerr
Solicitor
The Chifley Tower
2 Chifley Square
Sydney NSW 2000

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 735113 (87145/98). In the name of: Mundipharma Medical GmbH

- and -

OPPOSITION THERETO BY: Grunenthal GmbH under Section 59 of the Patents Act.

ANNEXURE

This is Annexure KFB-1 referred to in my Statutory Declaration made this 1st day of June 2005.

KENNETH FREDERICK BROWN

WITNESS: _____

Philip Kerr
Solicitor

Allens Arthur Robinson
Patent & Trade Marks Attorneys
Chifley Tower
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Sydney, NSW, 2000

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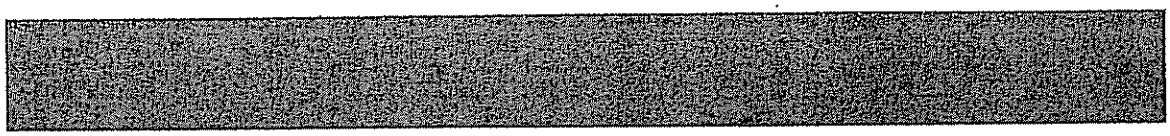

Present Address 209 Burraneer Road, Coomba, NSW. 2428

Date & Place of Birth 12 February 1942, Goulburn, NSW. Australia

Degrees

BPharm, University of Sydney, 1963
MPharm, University of Sydney, 1965
PhD, University of Sydney, 1968

Present Activities Consultant Pharmaceutical Scientist in Pharmaceutics – part time

Positions Held

1992-Apr 2000:	Professor of Pharmaceutics, Faculty of Pharmacy, College of Health Sciences, University of Sydney
1988-1992	Medical and Technical Director, 3M Pharmaceuticals, 3M Health Care Group, 9-15 Chilvers Road, Thornleigh NSW 2120
1976-1988	Senior Lecturer in Pharmaceutics, Department of Pharmacy, University of Sydney
1969-1976	Lecturer in Pharmaceutics, Department of Pharmacy, University of Sydney
1968	Postdoctoral Research Fellow, Department of Pharmaceutics, State University of New York at Buffalo, NY, USA
1966-1967	Research Student, supported by the Pharmaceutical Society of NSW, Research Trust, University of Sydney
1963-1965	Teaching Fellow, Department of Pharmacy, University of Sydney

Overseas Experience

1988-1992	While employed by 3M Pharmaceuticals, numerous overseas trips of 2 to 3 weeks duration for global R&D planning meetings in USA, and UK, Auckland, Tokyo, Singapore, Bangkok and Manila.
1985	Visiting Scientist (6 months), Departement de Pharmacologie, Faculte de Medecine, Universite de Paris XII, Creteil, Paris, France (0.5 yr)
1975	Visiting Lecturer, School of Pharmacy, University of Manchester, UK (1 yr)
1968	Postdoctoral Fellow, Department of Pharmaceutics, SUNY, Buffalo, NY, USA (1 yr)

Specialist Fields

Physical pharmaceutics; solids, liquids, disperse systems, surface chemistry;
Design, formulation and evaluation of pharmaceutical dosage forms;
Biopharmaceutics; pharmacokinetics; drug metabolism;
Inhalation aerosols;
Topical therapies;
Immunosuppressants.

Specific Research Areas

Inhalation drug delivery;
Biopharmaceutics, drug metabolism and pharmacokinetics of inhaled glucocorticoids;
Clinical pharmaceutics of immunosuppressant drugs in transplant recipients;
Plasma protein, blood binding of drugs and their influences on drug disposition;
Interactions between drugs and macromolecules of synthetic and biological origin;
Dissolution kinetics of drugs from solid oral dosage forms.

Research Supervision

I have supervised the research projects of twelve PhD graduates and co-supervised a further five PhD students and numerous MSc candidates.

Industry Experience

While employed at 3M Pharmaceuticals I was responsible for all technical and medical matters for the support of the company's marketed products and the development of new products for Australia, New Zealand and South East Asia. At the time of my resignation in 1992 I was manager of a department of 27 staff in 4 subsidiary departments.

Memberships

I have been a long term member of the following:

Pharmaceutical Society of Australia

Australasian Pharmaceutical Science Association (President 1992-1998)

Australasian Society for Clinical and Experimental Pharmacology and Toxicology

Australian Society for Medical Research

University of Sydney Club (President 1994)

PUBLICATIONS

Research Articles

1. Bjaastad, S.G. F, Brown, K.F. (1964). Z-Values and the solubilization of camphor by Tween 20. *Aust. J. Pharm.*, **45**, Suppl. 116s-117s.

2. Mitchell, A.G., Brown, K.F. (1966). Interaction of preservatives with cetomacrogol. *J. Pharm. Pharmac.*, **18**, 115-125.

3. Brown, K.F., Guttman, D.E. F, Anderson, A.S. (1969). Interference by surface-active agents with the 4-aminoantipyrine determination of hexachlorophene and other phenols. *J. Pharm. Sci.*, **58**, 1393-1398.

4. Crooks, M.J., Brown, K.F. (1973). A note on the solubilization of preservative mixtures by cetomacrogol. *J. Pharm. Pharmac.*, **25**, 281-284.

5. Brown, K.F., Crooks, M.J. (1973). Dynamic dialysis method for estimating the binding of preservatives to nonionic surfactants. *Pharm. Acta Helv.*, **48**, 494-503.

6. Crooks, M.J., Brown, K.F. (1973). Binding of sulphonylureas to serum albumin. *J. Pharm. Sci.*, **62**, 1904-1906.

7. Crooks, M.J., Brown, K.F. (1974). Competitive interactions of preservative mixtures with cetomacrogol. *J. Pharm. Pharmac.*, **26**, 235-242.

8. Crooks, M.J., Brown, K.F. (1974). Interaction of chloroxylenol and methyl p-hydroxybenzoate with sodium lauryl sulphate. *Aust. J. Pharm. Sci.*, **NS 3**, 93-94.

9. Crooks, M.J., Brown, K.F. (1974). Interaction of sulphonylureas with serum albumin. *J. Pharm. Pharmac.*, **26**, 304-311.

10. Brown, K.F., Crooks, M.J. (1974). Binding of sulphonylureas to serum albumin I I. The influence of salt and buffer composition on tolbutamide and glyburide. *Canad. J. Pharm. Sci.*, **9**, 75-77.

11. Page, M.A., Anderson, R.A., Brown, K.F., Roberts, M.S. (1974). The availability of sodium salicylate from enteric coated tablets. *Aust. J. Pharm. Sci.*, **NS 3**, 95-99.

12. Crooks, M.J., Brown, K.F. (1975). Interaction of glipizide with human serum albumin. Biochem. Pharmacol., **24**, 298-299.

13. Veng Pederson, P., Brown, K.F. (1975). Dissolution profile in relation to initial particle distribution. *J. Pharm. Sci.*, **64**, 1192-1195.

14. Veng Pederson, P., Brown, K .F. (1975). Size distribution effects in multiparticulate dissolution *J. Pharm. Sci.*, **64**, 1981-1986.

15. Veng Pederson, P., Brown, K.F. (1976). Isotropic dissolution of non-spherical particles. *J. Pharm. Sci.*, **65**, 1437-1442.

16. Veng Pederson, P., Brown, K.F. (1976). Experimental evaluation of three single-particle dissolution models for multiparticulate systems. *J. Pharm. Sci.*, **65**, 1442-1447.

17. Brown, K.F., Crooks, M.J. (1976). Displacement of tolbutamide, glibenclamide and chlorpropamide from serum albumin by anionic drugs. *Biochem. Pharmacol.*, **25**, 1175-1178.

18. Veng Pederson, P., Brown, K.F. (1977). General class of multiparticulate dissolution models. *J. Pharm. Sci.*, **66**, 1435-1438.

19. Veng Pederson, P., Crooks, M.J. & Brown, K.F. (1977). Method of obtaining drug-macromolecule binding parameters from dynamic dialysis data. *J. Pharm. Sci.*, **66**, 1458-1461.

20. Whitlam, J.B., Crooks, M.J., Brown, K.F., Veng Pederson, P. (1979). Binding of nonsteroidal anti-inflammatory agents to proteins. I. ibuprofen-serum albumin interaction. *Biochem Pharmacol.*, **28**, 678-683.

21. Whitlam, J.B., Brown, K.F. (1980). Computation of multiclass drug protein binding parameters. *Internat. J. Pharm.*, **5**, 49-58.

22. Whitlam, J.B., Brown, K.F. Crooks, M.J., Room, G.R.W. (1981). Transsynovial distribution of ibuprofen in arthritic patients. *Clin. Pharmacol. Ther.*, **29**, 487-492.

23. Whitlam, J.B., Brown, K.F. (1981) Ultrafiltration in serum protein binding determinations. *J. Pharm. Sci.*, **70**, 146-150.

24. Ridd, M.J., Brown, K.F., Moore, R.G., McBride, W.G., Nation. R.L. (1982). Diazepam plasma binding in the perinatal period: Influence of nonesterified fatty acids. *Eur. J. Clin. Pharmacol.*, **22**, 153-160.

25. Ridd, M.J., Brown, K.F., Moore, R.G., Nation, R.L. (1982). Drug plasma binding and nonesterified fatty acids: Methodologic considerations. *Internat. J. Pharmaceutics*, **11**, 11-20.

26. Walker, J.S., Shanks, C.A., Brown, K.F. (1983). Determinants of d-tubocurarine plasma protein binding in health and disease. *Anesth. Analg.*, **62**, 870-874.

27. Shanks, C.A., Ramzan. M.I., Walker, J.S., Brown, K.F. (1983). Gallamine disposition in open-heart surgery involving cardiopulmonary bypass. *Clin. Pharmacol. Ther.*, **33**, 792-799.

28. Walker, J.S., Shanks, C.A., Brown, K.F. (1983). Alcuronium kinetics and plasma concentration-effect relationship. *Clin. Pharmacol. Ther.*, **33**, 510-516.

29. Walker, J.S., Shanks, C.A., Brown, K.F. (1983). Alcuronium kinetics in patients undergoing cardiopulmonary bypass surgery. *Brit. J. Clin. Pharmacol.*, **15**, 237-244.

30. Asali, L.A., Nation, R.L., Brown, K.F. (1983). Determination of naloxone in blood by high-performance liquid chromatography. *J. Chromatog. Biomed. Applic.*, **278**, 329-335.

31. Ridd, M.J., Brown, K.F., Nation, R.L., Collier, C.B. (1983). Differential transplacental binding of diazepam: Causes and implications. *Euro. J. Clin. Pharmacol.*, **24**, 595-601.

32. Pearce, G.A., Brown, K.F. (1983). Heat inhibition of *in vitro* lipolysis and ^{14}C-ibuprofen protein binding in plasma from heparinized uraemic subjects. *Life Sciences*, **33**, 1457-1466.

33. Walker, J.S., Shanks, C.A., Brown, K.F. (1984). Altered disposition of d-tubocurarine during cardiopulmonary bypass surgery. *Clin. Pharmacol. Ther.*, **35**, 686-694.

34. Asali, L.A., Brown, K.F. (1984). Protein binding of naloxone in adult and foetal plasma. *Euro. J. Clin. Pharmacol.*, **27**, 459-463.

35. Evans, M.A., Shanks, C.A., Brown, K.F., Triggs, E.J. (1985). Pharmacokinetic and pharmacodynamic modelling with pancuronium. *Euro. J. Clin. Pharmacol.*, **26**, 243-250.

36. Gross, A.S., Brown, K.F. (1985). Plasma protein binding of ritodrine in Nnonpregnant women and at parturition. *Euro. J. Clin. Pharmacol.*, **28**, 479-481.

37. Evans, M.A., Brown, K.F., Imperial, E., Triggs, E.J. (1985). Pharmacokinetics of tocainide hydrochloride in healthy volunteers and elderly patients with ventricular arrhythmias. *J. Pharm. Pharmac.*, **37**, suppl. 38P.

38. Tett, S.E., Cutler, D.J., Brown, K.F. (1985). HPLC assay of hydroxychloroquine and metabolites in blood and plasma. *J. Chromatog. Biomed. Applic.*, **344**, 241-248.

39. Tett, S.E., Cutler, D.J., Brown, K.F. (1986). Removal of an endogenous fluorescent compound from urine to allow quantification of low concentrations of hydroxychloroquine and metabolites by HPLC. *J. Chromatog. Biomed. Applic.*, **383**, 236-238.

40. Gross, A.S., Brown, K.F., Lambert, J.A., Nation, R.L. (1987). Determination of ritodrine hydrochloride in blood and plasma by high-performance liquid chromatography with fluorescence detection. *J. Chromatog. Biomed Applic.*, **416**, 400-408.

41. Walker, J.S., Shanks, C.A., Borton, C., Brown, K.F. (1987). Alcuronium pharmacodynamics in dogs: effect-concentration relationships in the diaphragmatic and limb muscles. *J. Pharm. Pharmac.*, **39**, 614,-620.

42. Tett, S.E., Cutler, D.J., Day, R.O., Brown, K.F. (1988). Dose ranging study of the pharmacokinetics of hydroxychloroquine following intravenous administration to healthy volunteers. *Brit. J. Clin. Pharmacol.*, **26**, 303-315.

43. Tett, S.E., Cutler, D.J., Day, R.O., Brown, K.F. (1989). Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Brit. J. Clin. Pharmacol.*, **27**, 771-779.

44. Ridd, M.J., Brown, K.F., Nation, R.L. & Collier, C.B. (1996). The Disposition and Placental Transfer of Diazepam in Caesarean Section. *Clin. Pharmacol. Ther.*, **45**, 506-512.

45. Li, Y.N, Tattam, B. Brown, K.F., Seale, J.P. (1996). Determination of epimers 22R and 22S of budesonide in human plasma by high-performance liquid chromatography-atmospheric pressure chemical ionization mass spectrometry. *Journal of Chromatography B: Biomedical Applications*, **683**, 259-268.

46. Akhlaghi, F., McLachlan, A., Keogh, A., Brown, K. F. (1997). Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant *recipients*. *Br. J. Clin. Pharmacol.*, **44**, 537-542.

47. Li, Y.N,. Tattam, B.N., Brown, K.F., Seale, J.P. (1997). A sensitive method for the quantification of fluticasone propionate in human plasma by high-performance liquid chromatography/atmospheric pressure chemical ionisation mass spectrometry. *Journal of Pharmaceutical & Biomedical Analysis.*, **16**, 447-452.

48. Foe, K., Brown, K.F., Seale, J.P. (1998). Decomposition of beclomethasone propionate esters in human plasma. *Biopharmaceutics & Drug Disposition*, **19**, 1-8.

49. Foe, K., Cheung, H.T., Tattam, B.N., Brown, K.F., Seale, J.P. (1998). Degradation products of beclomethasone dipropionate in human plasma. *Drug Metabolism & Disposition*, **26**, 132-137.

50. Akhlaghi, F., Ashley, J.J., Keogh, A., Brown, K.F. (1998). Indirect estimation of the unbound fraction of cyclosporine in plasma. *Therapeutic Drug Monitoring*, **20**, 301-308.

51. Smith, K.J., Chan, H.-K., Brown, K.F. (1998). Influence of flow rate on aerosol particle size distributions from pressurized and breath-actuated inhalers. *Journal of Aerosol Medicine*, **11**, 231-245.

52. Akhlaghi, F., Keogh, A., Brown, K.F. (1999). Unbound cyclosporine and allograft rejection after heart transplantation. *Transplantation*, **67**, 54-59.

53. Akhlaghi, F., Ashley, J.J., Keogh, A., Brown, K.F. (1999). Cyclosporine plasma unbound fraction in heart and lung transplant recipients. *Therapeutic Drug Monitoring*, **21**, 8-16

54. Namkung-Matthai, H., Seale, J P., Brown, K., Mason, R. (1999). Comparative effects of anti-inflammatory corticosteroids in human bone-derived osteoblast-like cells. *European Respiratory Journal*, In press (accepted August 9, 1998).

55. Feddah, M., Brown, K.F., Gipps, E., Davies, N. (2000). In-vitro characterisation of metered dose inhaler versus dry powder inhaler glucocorticoid products: Influence of inspiratory flow rates. *Journal of Pharmacy and Pharmaceutical Sciences*, 3, (3): 317-324.

56. Foe, K., Cutler, D.J., Brown, K.F., Seale, J.P. (2000). Metabolism kinetics of beclomethasone propionate esters in human lung homogenates. *Pharmaceutical Research*, **17**, (8), 1007-1012.

57. Seeto, C., Namkung-Matthai, H., Jayrams, S., Foe, K., Brown, K.F, Hughes, J.M, Mason, R., Armour, C., Seale, J.P. (2000). Differential potency of beclomethasone esters *in vitro* on human T-lymphocye cytokine production and osteoblast activity. Journal of Pharmacy and Pharmacology, **52**, (4), 417-423.

58. Foe, K., Brown, K.F, Seale, J.P. (2000). Comparative kinetics of metabolism of beclomethasone propionate esters in human lung homogenates and plasma. *Journal of Pharmaceutical Sciences*, **89**, (9), 1143-1150.

59. Minto, C., Li, Y.N., Tattam, B., Brown, K., Seale, J.P, Donnelly, R. (2000). Pharmacokinetics of epimeric budesonide and fluticasone propionate after repeat dose inhalation – intersubject variability in systemic absorption from the lung. *British Journal of Clinical Pharmacology*, **50**, 116-124.

60. Feddah, M.R., Brown, K.F. Gipps,E M., Davies, N.M. (2000). In-vitro characterisation of metered-dose Inhaler versus dry powder inhaler glucocorticoid products: Influence of inspiratory flow rates. *Journal of Pharmacy and Pharmaceutical Sciences*, **3**, 317- 324

61. Teng, X.W., Foe, K., Brown, K.F, Cutler, D.J, Davies, N.M. (2001). High performance liquid chromatographic analysis of mometasone furoate and its degradation products. Application to *in vitro* degradation studies. *Journal of Pharmaceutical and Biomedical Analysis*, **26**, 313-319.

62. Li, Y., Tattam, B., Brown, K.F., Seale, J.P. (2001). Simultaneous quantification of epimeric budesonide and fluticosone propionate by liquid chromatography atmospheric pressure chemical ionisation tandem mass spectrometry. *Journal of Chromatography*: **B, 761**, *177-185*

63. Feddah, M.R., Brown, K.F., Gipps, E.M., Davies, N.M. (2001) Influence of respiratory spacer devices on aerodynamic particle size distribution and fine particle mass from beclomethasone metered dose inhalers *Journal of Aerosol Medicine*, **14, (4)** 477-485

64. Zahir, H., Nand, R.A., Brown, K.F., Tattam, B.N., McLachlan, A.J. (2001) Validation of methods to study the distribution and protein binding of tacrolimus in blood. *J. Pharmacol Toxicol Methods* **46,** 27-35

Reviews

65. Brown, K.F. (1970). Pharmaceutical reviews, 1969. *Aust. J. Pharm.*, **51**, suppl. s49-s54.

66. Brown, K.F. (1971). Anaemias and their treatment. *Aust. J. Pharm.*, **52**, 449-453.

67. Brown, K.F. (1971). Pharmaceutical reviews, 1970. *Aust. J. Pharm.*, **52,** suppl. s33-s39.

Abstracts and Presentations

1. Brown, K.F., Bjaastad, S.G. (1963). Measurement of z-values in solutions of nonionic surfactants, ANZAAS, Canberra.

2. Brown, K.F., Mitchell, A.G. (1966). Interaction of preservatives with cetomacrogol, ANZAAS, Melbourne.

3. Brown, K.F., Guttman, D.E., Anderson, A.S. (1969). Interference by colloidal materials with the 4-aminoantipyrine colorimetric method for estimating phenols, ANZAAS, Adelaide.

4. Brown, K.F. (1971). Some biopharmaceutical implications of complexation, ANZAAS., Brisbane.

5. Crooks, M.J., Brown, K.F. (1971). Interaction of preservative mixtures with a nonionic surfactant, ANZAAS, Brisbane.

6-8. I co-authored three papers presented by others at ANZAAS in Perth (1973).

9. Brown, K.F., Elworthy, P.H. (1977). Fluorescent probes in surfactant systems, Aust. Pharm. Sci. Assoc., Melbourne.

10. Whitlam, J.B., Crooks, M.J., Brown, K.F. (1977). Studies on serum protein binding of ibuprofen, Aust. Pharm. Sci. Assoc., Melbourne.

11. Whitlam, J.B., Brown, K.F. (1979). Ultrafiltration and equilibrium dialysis - their reliability in whole serum binding, Aust. Sci. Clin. Exp. Pharmacol., Otago, NZ.

12. Ridd, M.J., Moore, R.G., Brown, K.F., McBride, W.G. (1979). Influence of labour on the plasma protein binding of diazepam in humans, Aust. Sci. Clin. Pharmacol., Otago, NZ.

13. *Brown, K.F (1979) Dissolution methodology. Invited lecture to National Symposium on Dissolution Testing conducted by Aust. Pharm. Sci. Assoc., (Nov.)

14. Olsen, W.A.,Brown, K.F. (1980) Dynamic dialysis of aqueous chlorhexidine diacetate solutions. Abstract *Aust. J. Pharm. Sci.*, **9**, 54.

15. Brown, K.F., Ridd, M.J., Nation, R.L., Moore, R.G., McBride, W.G. (1980) Diazepam binding

in the plasma of parturient women. Abstract *Aust. J. Pharm. Sci.*, **9**, 56.

16. Whitlam, J.B., Brown, K.F., Crooks, M.J. (1980) Transsynovial distribution of ibuprofen in arthritic patients. Abstract *Aust. J. Pharm. Sci.*, **9**, 58.

17. Pearce, G.A., Brown, K.F. (1981) Plasma binding of ibuprofen in uraemia and haemodialysis. Abstract *Aust. J. Pharm. Sci.*, **10**, 47.

18. Whitlam, J.B., Brown, K.F. (1981) Thermodynamic analysis of arylpropionic acid anti-inflammatory drug interactions with human serum albumin. Abstract *Aust. J. Pharm. Sci.*, **10**, 46.

* invited presentation

19. Ridd, M.J., Brown, K.F., Moore, R.G., Nation, R.L. (1981) Artefacts in blood and plasma handling in binding methods. Abstract *Aust. J. Pharm. Sci.*, **10**, 46.

20. Walker, J.S., Shanks, C.A., Brown, K.F. (1981) Alcuronium kinetics during cardiopulmonary bypass. Abstract *Aust. J. Pharm. Sci.*, **10**, 49.

21. Pearce, G.A., Brown, K.F., Roberts, D.C.K. (1982) Heparin activated lipolysis in haemodialysis and quinidine plasma binding. Aust. Pharm. Sci. Assoc., Sydney.

22. Olsen, W.A., Brown, K.F. (1982) Dialysis kinetics of chlorhexidine salts in aqueous solutions of electrolytes. Aust. Pharm. Sci. Assoc., Sydney.

23. Asali, L.A., Brown, K.F., Nation, R.L. (1982) Analysis of naxolone in the blood of apnoeic infants. Aust. Pharm. Sci. Assoc., Sydney.

24. Roberts, D.C.K., Pearce, G. A., Brown, K.F. (1982) Uraemic hypertriglyceridaemia:associations with drug binding. Australian Atheroscierosis Group, 9th Annual Scientific Meeting, Melbourne, May.

25. Gross, A.S., Brown, K.F. (1983) Plasma protein binding of ritodrine. Aust. Pharm. Sci. Assoc., Perth.

26. Asali, L.A., Brown, K.F. (1983) Naxolone binding in adult and foetal plasma. Aust. Pharm. Sci. Assoc., Perth.

27. Asali, L.A., Brown, K.F., Handelsman, D.J., Fiamer, H.E. (1984) Absence of cardiovascular effects of high dose naxolone in healthy and uraemic subjects. Aust. Soc. Clin. Exp. Pharmacol. Melbourne.

28. Gross, A.S., Baird-Lambert, J.A., Brown, K.F. (1985) Distribution of ritodrine in whole blood at parturition. Aust. Soc. Clin. Exp. Pharmacol., Brisbane (1985).

29. Tett, S.E., Cutler, D.J., Brown, K.F., Day, R.O. (1985) Hydroxychloroquine pharmacokinetics:the importance of experimental design. Aust. Pharm. Sci. Assoc., Brisbane.

30. Brown, K.F., Evans, M.A., Imperial, E., Triggs, E. J. (1985) Pharmacokinetics of tocainide hydrochloride in healthy volunteers and elderly patients with ventricular arrhythmias. Presented to Brit. Pharm. Conf., Leeds (Sept).

31. * Research Seminar: Drug plasma protein binding and its influence on the distribution of ibuprofen and diazepam. Departement de Pharmacologie, Faculte de Medecine, Universire de Paris XII, Creteil, Paris (Nov 1985) [contact Prof. J.P. Tillement].

32. Research Seminar: Drug plasma protein binding: The influence of stress and disease conditions. School of Pharmacy, University of Leuven, B-3000 Leuven, Belgium (Dec. 1985) [contact Prof. Renaat Kinget, Campus,G. asthuisberg O & N].

33. * Research Seminar: (Title as for 32), School of Pharmacy, Brighton Polytechnic, Brighton, UK (13th Jan. 1986) [contact Dr C. Marriott].

34. Research Seminar: (Title as for 32), School of Pharmacy, the University of Bath,Bath, UK (l4th Jan. 1986) [contact Prof. John Rees].

* invited presentation

35. * Research Seminar: (Title as for 32), The Welsh School of Pharmacy, University of Cardiff, UK (17th Jan. 1986) [contact Prof. I. Kellaway].

36. * Drug plasma protein binding in disease and pregnancy. Conference on Albumin Structure and Function, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Utrecht 113th Feb. 1986) [organiser Prof. L.H.M. Janssen].

37. * Research Seminar: (Title as for 32), Faculte de Farmacie, Laboratoire de Biophysique, Universite d'Aix-Marseille 2, Marseille, France, 17th Feb. 1986 as part of a 2 day visit [contact Prof. Claudette Briand]

38. * Brown, K.F. Influence of disease and stress conditions on the plasma protein binding of drugs. General overview presented to Alumni Association, Pharmacy Practice Foundation, University of Sydney (10th June, 1986).

39. * Brown, K.F. Methodology for the determination of plasma drug concentrations. Presentation to IVth Annual Symposium on Advances in Therapeutic Drug Monitoring, Sebel Town House. Organised by the Department of Clinical Pharmacology, University of New South Wales (October, 1986).

40. * Brown, K.F. Dissolution testing - Why bother? Does 'bio-inequivalence' exist? Presentation to Symposium on Questions in Pharmaceutical Analysis. Roy. Aust. Chem. Inst., Pharm, Sci, Grp.. (25th March, 1987).

41. Tett, S.E., Cutler, D.J., Brown, K.F., Day, R.O. (1987) Bioavailability of hydroxychloroquine. IUPHAR - World Congress of Pharmacology - Sydney, August.

42. Li, Y.N., Tattam, B., Brown, K.F., Seale, J.P. Determination of 22R,S epimers of glucocorticosteroid budesonide in human plasma by HPLC, *Proceedings of the Australasian Society of Clinical & Experimental Pharmacologists and Toxicologists (ASCEPT)*, December, 1994, Auckland, New Zealand.

43. Li, Y.N., Tattam, B, Brown, K.F., Seale, J.P. Plasma protein binding of glucocorticsteroid budesonide. *Australasian Pharmaceutical Science Association (APSA)*, December, 1994, Auckland, New Zealand.

44. Li, Y.N., Tattam, B., Brown, K.F., Seale, J.P. Determination of (22R,S) budesonide in human plasma by liquid chromatography-atmospheric chemical ionization mass spectrometry. *Proceedings of the Australasian Society of Clinical & Experimental Pharamcologists and Toxicologists (ASCEPT)*, December, 1995, Adelaide, Australia.

45. Foe, K. and Brown, K. F. A kinetic study of the degradation of beclomethasone propionate esters *in vitro*. Oral presentation, *The Australian Pharmaceutical Associations (APSA)*

Scientific Meeting, December 1995, Adelaide, Australia. Abstract published in *The Australian Journal of Hospital Pharmacy*, **26**, 511 (1996).

46. Li, Y.N., Tattam, B., Brown, K.F., Seale, J.P. A sensitive method for quantification of fluticasone propriate in human plasma by high-performance liquid chromatograph-atmospheric chemical ionization mass spectrometry. *Australasian Pharmaceutical Science Association (APSA)*, December, 1996, Melbourne, Australia.

* invited presentation

47. Foe, K., Tattam, B., Cheung, H.T., Seale, J.P., Brown, K.F. Identification and characterisation of degradation products of beclomethasone dipropionate in human plasma. Poster presentation, *The Australasian Pharmaceutical Science Association (APSA) Scientific Meeting*, December, 1996, Melbourne, Australia. Abstract published in *The Australian Journal of Hospital Pharmacy*, **26,** (suppl. 1), S46 (1996).

48. Winning, J., Awad, V., Campbell, D., Brown, K.F. Current research-syringe driver admixtures. Policy and Practice. *South-Eastern Region Branch of the Association of Palliative Care Nurses Conference* Diversity in palliative care. Held at Rydges Resort Eagle Hawk Hill, Canberra, 6th December 1996.

49. Awad, V., Brown, K.F., Campbell, D., Winning, J. The stability and compatibility of morphine sulphate injection and other injectable drugs used in palliative care. *Australian Journal of Hospital Pharmacy*, **26,** (suppl 1), December 1996.

50. Winning, J., Awad, V., Campbell, D., Brown, K.F. The stability and compatibility of injectable drug combinations in palliative care: Rational guidelines for use. *Australian Association for Hospice and Palliative Care Inc.* 4th National Conference, National Convention Centre, Canberra, 17-19th September 1997.

51. Awad, V., Brown, K.F., Campbell, D., Winning, J., The stability and compatibility of morphine sulphate with injectable drug formulations used by subcutaneous infusion in palliative care. *Australian Society of Hospital Pharmacists,* 23rd Federal Conference, Adelaide, 13-17th November 1997

52. Li, Y.N., Tattam, B., Brown, K.F., Seale, J.P. Pharmacokinetic profiles of epimeric budesonide and fluticasone propionate in healthy subjects. *Australasian Pharmaceutical Science Association (APSA),* December 1997, Sydney, Australia.

53. Foe, K., Brown, K.F , Seale, J.P. Comparative kinetics of metabolism of beclomethasone proplonate esters in human plasma and lung cytosol *in vitro*. Oral presentation, *The Australasian Pharmaceutical Science Association (APSA) Scientific Meeting*, December 1997, Sydney, Australia. Abstract published in *The Scientific Program and Abstracts Book of APSA*, **35** (1997).

54. Foe, K., Cutler, D.J., Brown, K.F., Seale, J.P. Kinetics of beclomethasone propionate esters in human lung cytosol *in vitro*. Oral presentation, *The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) 31st Annual Scientific Meeting*, December 1997, Canberra, Australia. Abstract published in *The Proceedings of ASCEPT*, **4**, 36 (1997).

55. Foe, K., Cutler, D.J., Brown, K.F., Seale, J.P. Interindividual variability in activation of

beclomethasone dipropionate in human lung cytosol *in vitro*. Poster presentation, *The Thoracic Society of Australia & New Zealand (TSANZ) Annual Scientific Meeting*, March 1998, Adelaide, Australia. Abstract published in *The Program and Abstracts Book of TSANZ*, P23 (1998).

56. Brown, K.F., Foe, K., Cutler, D.J., Seale, J.P. Metabolism kinetics at beclomethasone propionate esters in human plasma and lung cytosol *in vitro*. Oral presentation, *2nd World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology APGI/APV*, May 1998, Paris, France.

57. Teng, X.W., Foe, K., Brown, K.F. Investigations of metabolism kinetics of mometasone furoate in human lung and plasma *in vitro*. Oral presentation, *The College of Health Sciences and The Medical Foundation Research Conference*, October 1998, Leura, Australia

58. Foe, K., Brown, K.F., Seale, J.P. Metabolism kinetics of beclomethasone propionate esters in human liver and lung *in vitro*. Oral presentation, *The College of Health Sciences and The Medical Foundation Research Conference*, October 1998, Leura, Australia. Abstract published in *The Conference Book*, 23-25, (1998).

59. Foe, K., Cutler, D.J., Brown, K.F., Seale, J.P. Characterisation of the kinetics of beclomethasone propionate esters in human liver *in vitro*. Oral presentation, *Conjoint Meeting of the The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and The Australasian Pharmaceutical Association (APSA)*, December 1998, Hobart, Australia. Abstract published in *The Proceedings of ASCEPT*, 5, 34, (1998).

60. Foe, K., Cutler, D.J., Brown, K.F. Seale, J.P. Comparative metabolism kinetics of beclomethasone propionate esters in human liver, lung and plasma *in vitro*. Oral presentation, *Conjoint Meeting of the The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and The Australasian Pharmaceutical Association (APSA)*, December 1998, Hobart, Australia. Abstract published in *The Proceedings of ASCEPT*, 5,62, (1998).

61. Teng, X.W., Foe, K., Brown, K.F. Metabolism kinetics of mometasone furoate in human lung and human plasma *in vitro*. Poster presentation, *Conjoint Meeting of the The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and The Australasian Pharmaceutical Science Association (APSA)*, December 1998, Hobart, Australia. Abstract published in *The Proceedings of ASCEPT*, 5, 101 (1998).

62. Foe, K., Brown, K.F., Seale, J.P. Metabolism kinetics of beclomethasone propionate esters in the homogenates of human lung and liver, whole blood and plasma *in vitro*. Poster presentation, *The Thoracic Society of Australia & New Zealand (TSANZ) Annual Scientific Meeting*, March 1999, Canberra, Australia. Abstract published in *Respirology*, **4** (suppl.), A26 (1999).

In addition to those listed above, I have presented research seminars to the Departments of Pharmacy at the Universities of Manchester, Queensland and Tasmania, Department of Pharmacology, and the Heart Research Institute, University of Sydney and the Departments of Biomedical Engineering and Clinical Pharmacology at the University of New South Wales. I have been a member of the NH&MRC's panel of assessors and I have served as referee for a number of journals including J. Pharmacokin. Biopharm., J. Pharm. Pharmac., Life Sciences, Aust. J. Pharm. Sci. and Aust. J. Hosp. Pharm.

I was President of the Australasian Pharmaceutical Science Association from 1992 to 1998 and was convenor of the organising committee of the two day International Conference, "Advances in the Delivery of Therapeutic and Diagnostic Agents" in December, 1992. The latter meeting was jointly sponsored by the international Controlled Release Society, the Australasian Pharmaceutical Scientists Association, the Royal Australian Chemical Institute, had numerous international speakers and about 160 participants.

EXHIBIT J

Translation from New Zealand

NEW ZEALAND PATENTS ACT 1953

Document #: 123971

IN THE MATTER OF New Zealand Patent Application No. 260408 in the name of Euro-Celtique S.A.

AND

IN THE MATTER of an Opposition under Section 21 by Grünenthal GmbH

COUNTER STATEMENT

We, Euro-Celtique S.A., of 122 Boulevard de la Petrusse, Luxembourg, respond to the opposition of Grünenthal GmbH against our New Zealand Patent Application 260,408 in the following terms:

Interest

1. The interest of the opponent as a potential infringer is not denied.

Novelty

2. The claimed invention has novelty. In each of EP 147780, US 5073379 or US 3065143 there is no disclosure of a product in accordance with any one of claims 1 to 16, 34, or 35, nor is there a disclosure of a process in accordance with any one of claims 17 to 33 or 36. More particularly, none of the cited documents discloses a controlled release tramadol product having the specified in-vitro dissolution rate characteristics.

2.0 Tramadol is a known analgesic which was invented by the Opponent in the 1960's and which has been marketed since 1977. Until the present invention, it was always a normal release preparation, where highly soluble tramadol hydrochloride is quickly released and rapidly assimilated into the body to provide relief of acute pain. In contrast, the present invention provides a controlled release form of tramadol which can be formulated as a product to be given twice or once a day, to provide longer pain relief. Claim 1 defines the product in the following manner:

> "A controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration, having an in-vitro dissolution rate (measured as herein defined) as set forth below:

TIME	% RELEASED (BY WEIGHT)
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100

16	30-100
24	50-100
36	>80

".

Nothing turns on the point, but we assert that this claim and the other claims are entitled to a priority date which is earlier than the date on which the complete specification was filed. Claim 34 clearly takes the first priority date of 10 May 1993, and in general the remaining claims take the third date of 09 March 1994. The Opponent advances no reason for denial of entitlement to priority, and without substantiation his denial must be set aside.

2.1 The cited EP 147780 describes and claims a composition of matter for oral, rectal or vaginal administration comprising a core tablet or granules of a therapeutically effective amount of at least one therapeutic agent selected from various specified classes of agents, and a polyvinyl coating on the core tablet or granules, with the amounts of therapeutic agent and polyvinyl alcohol falling within given ranges. Tramadol is mentioned in a very long list of possible therapeutic agents, but is not employed in any of the examples. There is no data in the specification relating to *in vitro* dissolution rates. The Applicants will show by evidence that a practical attempt to prepare a composition in accordance with the teaching of EP 147780, and using tramadol, gives a product with no real sustained release properties. More specifically, the Applicants will show that the teaching in EP 147780 gives a controlled release preparation for which the *in vitro* dissolution

rate does not fall within the ranges given in Claim 1 and does not fall within the other independent claims of the present patent application. Accordingly, EP 147780 does not anticipate the present invention.

2.2 US 5073379 describes the continuous preparation of solid pharmaceutical forms. The process is essentially directed at a more efficient process for producing already known formulations based on extruded polymer melts containing an active compound. The process is not directed especially at controlled release products. Tramadol is mentioned as a possible active compound among a list of about two hundred active compounds, but there is no example which employs tramadol. The formulations of this document are not particularly concerned with controlled release, as can be seen from the data given in Table 1 where the majority of the formulations prepared are rapid or instant release. There is no disclosure in this document that tramadol is to be used to prepare a controlled release formulation, and in particular there is no disclosure that tramadol is to be used to prepare a formulation with a particular release rate. Accordingly, US 5073379 does not anticipate the present invention.

2.3 US 3065143 relates to a sustained release tablet. There is no mention of tramadol. Accordingly there is no way in which the disclosure of US 3065143 can anticipate the present invention.

2.4 We can be certain of the novelty of the present invention by applying the notional infringement test. None of EP 143780, US 5073379 or US 3065143 contains a clear description of, or clear instructions to do or make, something that will infringe the present claims if carried out after the grant of the patent. It can not be said that carrying out the directions contained in the prior art will inevitably result in something being made or done which will constitute an infringement of the present claims. There is therefore no lack of novelty. Indeed, there is no signpost upon the road towards the present invention, and certainly it can not be said that any of the prior art documents have planted a flag at the destination which is now claimed. The invention is novel.

Inventive Step

3. The claimed invention involves an inventive step. Nothing in EP 147,780, US 5073379, US 3065143, GB 2196848, GB 1405088, EP 249347 or Page 1306, section 6233-w of Martindale The Extra Pharmacopoeia, 29th edition (1989) leads the skilled man to the claimed invention. There has been no prior use in New Zealand which leads the skilled man to the claimed invention.

3.0 Inventive step can not be in doubt. Tramadol has been commercially available for a long time. Controlled release compositions of other drugs have been commercially available for

a long time. There was nothing which indicated that it was obvious to produce a controlled release tramadol which was suited for at least 12-hourly dosing. Why choose to work with tramadol? When properly viewed at the priority date of the present invention, there is no disclosure in the cited references which indicates to the skilled man that the way forward is to make a tramadol preparation in accordance with the present invention. It is only with knowledge of the present invention that it becomes possible to point to certain passages among the literature, and attempt to construct an argument. As the Applicants will demonstrate, there was literature on tramadol where the whole emphasis was on normal release preparations, and there was a wealth of literature on controlled release preparations where there was no suggestion to employ tramadol. There is no recommendation that tramadol is the suitable candidate for the production of a controlled release preparation.

3.1 The cited EP 147,780 concerns a proposal for preparing a drug delivery system which uses polyvinyl alcohol as a coating material. Tramadol is mentioned in EP 147780, but only as one possible drug in a list encompassing five hundred or more active substances. Further, none of the Examples employs tramadol. Tramadol occurs simply as a passing mention in a shopping list and is not being presented seriously as a potential candidate for formulation. There is no reason except knowledge of the present invention which will lead the skilled person to pick out tramadol from the

other listed drugs. Indeed, as we have mentioned at paragraph 2.1, the Applicants will show by evidence that a practical attempt to prepare a composition in accordance with the teaching of EP 147780, and using tramadol, gives a product with no real sustained release properties. The teaching of EP 147780 does not provide an effective controlled release tramadol preparation, and it surely does not begin to point the skilled man towards the present invention.

3.2 US 5073379 is even further from the present invention. Indeed, although the Opponent includes this document among those cited against inventive step, he refers to it only once in the paragraphs 23 to 69 of his Statement of Case. For the time being, we observe that there really is nothing in US 5073379 which might point the skilled man to arrive at the present invention. US 5073379 is concerned with the continuous preparation of solid pharmaceutical forms, and it does not give to the skilled man any indication that he might achieve a commercially important product by preparing a controlled release tramadol preparation.

3.3 US 3065143 describes a wide variety of formulations with a wide variety of *in vitro* release rates, some of which may fall within the presently claimed release rate range. There is nothing in this US specification which suggests the use of tramadol as an active ingredient, and there is certainly nothing which leads to the present invention. As is evident from US 3065143, controlled

release matrix materials have been known since 1970. Tramadol is even older. It is surely indicative of an inventive step that the techniques for making controlled release formulations have been available for so long, and yet no one had conceived of the idea of employing tramadol to give an effective preparation suited for at least 12-hourly dosing. Indeed, tramadol is a compound which was very familiar to the Opponents who had extensive knowledge of its potential and characteristics, and yet with the wide dissemination of the techniques for making controlled release formulations, they did not see the possibility of making an effective controlled release tramadol preparation. In short, if the invention was obvious, why was the invention not made earlier? More especially, why was the invention not made and disseminated by the Opponent?

3.4 GB 2196848 is concerned with a controlled release hydromorphone preparation. The fact that similar matrixes and similar release profiles might be known for hydromorphone provides no scientific basis for alleging that it was obvious to employ them for a tramadol preparation. The Applicants will produce evidence to show that it is a facile simplification to place emphasis on the similarity in solubility of hydromorphone hydrochloride and tramadol. To the contrary, there are a wide variety of factors which influence the pharmacokinetic and pharmacodynamic balance of a drug and which determine whether a particular *in vitro* release profile will give a desired effectiveness *in vivo*.

Identical *in vitro* rates for different drugs do not guarantee identical *in vivo* performance profile. Until the present patent application was published, there was no way to know what *in vitro* dissolution rates for tramadol might give 12 hour to 24 hour *in vivo* analgesic effect. Having regard to their respective pharmacokinetic and pharmacodynamic performances, there is no justification for relying upon the release profiles of formulations of hydromorphone hydrochloride to predict what *in vitro* release rate for tramadol might be suited for a 12 hour analgesic effect. Put bluntly, it is not possible to predict that a desired *in vivo* performance will be achieved by adoption of a given *in vitro* release rate. Moreover, the focus on any similarity of release rates does not in itself provide any sound basis for asserting that it was obvious to manufacture a preparation in accordance with the present invention. What in the prior art points the skilled man to the present invention?

3.5 GB 1405088 concerns a slow release formulation and was published in 1975. It does not advance the case of the Opponent in any way. More specifically, there is nothing in GB 1405088 which provides the missing impetus to elect to take the drug tramadol and to prepare a controlled release preparation in accordance with the present invention.

3.6 EP 249347 is a controlled release dihydrocodeine composition. As with hydromorphone, there is no scientific basis for asserting that the use of a known formulation of a narcotic opioid such as dihydrocodeine will be appropriate for an entirely different, non-narcotic compound such as tramadol.

3.7 Page 1306, section 6233-w of Martindale The Extra Pharmacopoeia, 29th edition (1989) reports that hydromorphone hydrochloride has a solubility in water of 1 in 3. Such knowledge of water solubility in no way provides a reason to equate tramadol with hydromorphone hydrochloride when it comes to a consideration of formulating a controlled release preparation. Although solubility is a factor, it is only one factor among many others, including dissociation constants, partition coefficients, drug distribution between compartments, possible active metabolites and so forth. The argument presented by the Opponent is simplistic and based on pure hindsight. Even then, to raise such an argument misses the crucial point. Prior to the date of the present patent application, the skilled man had not considered tramadol to be a drug suited for formulating as a controlled preparation for use at least 12-hourly.

3.8 Thus, the inventive concept is a controlled release preparation of tramadol for at least 12 hour administration. To this end, the release is tailored to provide appropriate levels of pain relief to the recipient over the time period. Before the invention, no-one had

appreciated that a particularly useful preparation might be made using tramadol.

The Opponent has not cited any document which addresses, discloses or even foreshadows the relationship between *in vitro* release and desired *in vivo* activity. Accordingly any combination of documents relied upon by the opponent will be void of this particular feature. The applicant has identified an area of subject matter in which improved and useful results may be obtained. The invention is not obvious.

3.9 No details have been given of the prior use in New Zealand upon which the Opponent seeks to rely. In the absence of proof, there can be no case to answer that the invention might be obvious in the face of such a use. For the present, we assert that the present invention has an inventive step over any prior use which might be proved.

Invention

4. The subject of each claim of the complete specification is an invention within the meaning of the Act. There is no strength in the points raised by the Opponent, and there can be no doubt that the claimed product, and the claimed process, is related to a

manner of new manufacture within the meaning of Section 2 of the Act. The claimed subject matter is a not mere collocation, and is substantially more than a mere admixture of non-co-operating components. We will provide evidence to show that the claimed subject matter relates to a new and useful vendible product.

Description

5. The complete specification sufficiently and fairly describes the invention and the method by which it is to be performed.

5.1 The pedantic points raised by the Opponent do not truly go to the adequacy of the description for a skilled man who is minded to succeed in making an effective controlled release tramadol preparation. Indeed, in attempting to attack the description, the Opponent is effectively contradicting what he has to say in relation to lack of inventive step. The specification is to be read by the skilled man. Given his familiarity with the general technique of preparing controlled release preparations, and given the guidance provided in the present specification, there is no difficulty to perform the invention of the Claims.

5.2 The Applicants will provide evidence to show that the complete specification can be clearly understood by the skilled person who can draw upon his common general knowledge and upon the description in the present patent application.

Request

6. We ask for the opposition to be dismissed, and for grant of Letters Patent. We also request an award of costs in favour of the Applicant.

EXHIBIT K

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February 5, 2008

Robert E. Colletti
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VIA ELECTRONIC MAIL

Sona De, Esq.
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1211 Avenue of the Americas
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Re: *Purdue et al. v. Par Pharmaceutical et al.*
FLH Reference No. 540572-521

Dear Sona:

We are in the process of reviewing the large volume of documents produced by Purdue and Napp. Unfortunately, it does not appear that Purdue and Napp produced all documents responsive to our requests. We do not appear to have the documents identified below. If these documents were produced, please identify them by production number. If these documents were not produced, please produce them or explain why they are being withheld.

- The two abandoned patent applications which claim the benefit of the patent-in-suit and their prosecution histories, i.e., U.S. Patent Application Nos. 09/239,092 and 09/507,806.

- The prosecution histories for each corresponding foreign counterpart of the patent-in-suit. We note that certain foreign counterpart patents to the patent-in-suit have been produced but without their corresponding file histories.

- The November 25, 1998 expert report of Professor Alexander Florence. We have located Professor Florence's supplemental report, but not the initial expert report.

- The July 8, 1994 tramadol license agreement between Grunenthal GmbH and G.D. Searle & Co. Ltd. An amendment to this agreement has been produced (NAPP044052), but the original agreement has not been located.

Finally, please confirm that Purdue and Napp produced all documents from foreign litigations related to controlled-release tramadol. For example, we have not located the complete files from

the *Napp Pharmaceutical Group Ltd. v. Asta Medica Ltd.* U.K. litigation and the *Temmler Pharma GmbH v. Euro-Celtique S.A.* German litigation.

Sincerely,

Robert E. Colletti

Robert E. Colletti

cc: Frederick L. Cottrell, Esq.
Mary W. Bourke, Esq.
Richard D. Kirk, Esq.

EXHIBIT L

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February 11, 2008

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VIA ELECTRONIC MAIL
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Sona De, Esq.
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New York, New York 10036

Re: *Purdue et al. v. Par Pharmaceutical et al.*
FLH Reference No. 540572-521

Dear Sona:

This is a follow-up to my February 5, 2008 letter (copy attached) regarding deficiencies in the Purdue/Napp document production. Further to my letter it has become apparent that Purdue/Napp has not produced the full scope of documents from foreign litigations involving controlled-release tramadol. As just one example, Napp has not produced all the exhibits to the supplemental expert report of John Tasker Fell. Please let me know when we can expect a response to my initial letter

Sincerely,

Robert E. Colletti

Robert E. Colletti

Encl.
cc: Frederick L. Cottrell, Esq. (e-mail only)
Mary W. Bourke, Esq. (e-mail only)
Richard D. Kirk, Esq. (e-mail only)
Robert J. Goldman, Esq. (e-mail only)

EXHIBIT M

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February 21, 2008

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Re: *Purdue et al. v. Par Pharmaceutical et al.*
FLH Reference No. 540572-521

Dear Counsel:

My February 5 and February 11 letters regarding deficiencies in the Purdue/Napp ("Purdue") document production remain unanswered. It appears that the requested abandoned CIP patent applications as well as the initial report of Professor Florence were produced in the documents we subpoenaed from Davidson, Davidson & Kappel. We still await responses, however, to our other concerns. Please identify by production number the prosecution history for each corresponding foreign counterpart of the patent-in-suit or explain why these documents are being withheld. The prosecution history for the German priority document, namely DE 43 15 525, should be produced immediately. Moreover, please confirm that plaintiffs have produced all documents from foreign litigations and oppositions related to controlled-release formulations of tramadol.

Next Monday, we intend to file a motion requesting Judge Farnan to issue a Letter of Request. The Letter of Request seeks a deposition of Eric-Paul Paques of Grunenthal GmbH and certain documents. Please let us know by 12:00 p.m. on Monday if the plaintiffs will oppose this motion.

Attached is a courtesy copy of a subpoena for documents that we are today serving on Grunenthal USA Inc. Also attached is a Rule 30(b)(6) notice of deposition to Biovail. Finally, enclosed are notices of deposition for Robert Kaiko and Benjamin Oshlack.

Before we notice the depositions of the inventors listed on the face of the patent-in-suit I would like to discuss the location and timing of the depositions. It was previously indicated that these depositions would take place in the UK and Germany. Please let me know a convenient time for a short telephone conference on Monday next week.

Sincerely,

Robert E. Colletti

Robert E. Colletti

Enclosures
cc: Frederick L. Cottrell, Esq. (with enclosures)
Rodger D. Smith II, Esq. (with enclosures)

EXHIBIT N

Mar 12 15:47:50 EST 2008

THOMSON DELPHION

US6254887 Family Legal Status Report - 340 members found

Codes shown: **All** | Positive | Negative

Jump	Publication	Title	Filed	ApplNo
	ZA9502013A	PHARMACEUTICAL PREPARATION	1995-03-10	ZA1995000002103
	ZA9409296A	Sustained release compositions and a method of preparing pharmaceutical compositions	1994-11-23	ZA1994000009296
	ZA9407742A	Orally administrable opioid formulations having extended duration of effect	1994-10-04	ZA1994000007742
	ZA9404773A	Sustained release compositions and a method of preparing pharmaceutical compositions and a method of preparing pharmaceutical compositions	1994-07-01	ZA1994000004773
	ZA9404599A	Opioid formulations having extended controlled release	1994-06-27	ZA1994000004599
	ZA9402959A	Controlled release formulation	1994-04-28	ZA1994000002959
	ZA9206587A	Stabilized controlled release formulations having acrylic polymer coating	1992-07-29	ZA1992000006587
	ZA9201366A	STABILIZED CONTROLLED RELEASE SUBSTRATE HAVING A COATING DERIVED FROM AN AQUEOUS DISPERSION OF HYDROPHOBIC POLYMER	1992-02-25	ZA1992000001366
Status	US20060269603A1	Controlled release tramadol formulations	2006-05-16	US2006000435015
	US20030054032A1	Stabilized controlled release substrate having a coating derived from an aqueous dispersion of hydrophobic polymer	2001-11-12	US2001000054726
	US20020081333A1	Orally administrable opioid formulations having extended duration of effect	2001-06-26	US2001000891882
Status	US20010036477A1	Controlled release tramadol formulation	2001-03-06	US2001000800204
	US20010019725A1	Sustained release compositions and a method of preparing pharmaceutical compositions	2000-12-19	US2000000740732
Status	US7074430	Controlled release tramadol tramadol formulation	2001-03-06	US2001000800204
	US6572885	Orally administrable opioid formulations having extended duration of effect	2001-06-26	US2001000891882
	US6326027B1			
Status	US6326027	Controlled release formulation	1995-05-24	US1995000449772
	US6316031B1			
	US6316031	Stabilized controlled release substrate having a coating derived from an aqueous dispersion of hydrophobic polymer	1999-12-22	US1999000469478
	US6294195	Orally administrable opioid formulations having extended duration of effect	1999-09-07	US1999000390719
	US6254887B1			
Status	**US6254887**	Controlled release tramadol	1996-07-10	US1996000677798
	US6162467	Sustained release compositions and a method of preparing pharmaceutical compositions	1999-08-09	US1999000370270
	US6143353	Controlled release formulations coated with aqueous dispersions of acrylic polymers	1997-03-11	US1997000816023
	US6143328	Sustained release compositions and a method of preparing pharmaceutical compositions	1999-03-08	US1999000264399
Status	US6143322	Method of treating humans with opioid formulations	1997-04-08	US1997000838368

2005-10-28	RENW +	Renewal
2002-11-22	RENW +	Renewal

NO0942477A:

Gazette date	Code	Description (remarks) List all possible codes for NO
2002-11-04	FC2A -	Printed rejected and laid open patent application

NO0313124B1:

Gazette date	Code	Description (remarks) List all possible codes for NO
2006-01-23	ERR	Erratum (I PATENTTIDENDE NR 01/05 BLE PATENT NR 313124 FEILAKTIG KUNNGJORT TRADT UT AV KRAFT. PATENTET ER FORTSATT I KRAFT) (I PATENTTIDENDE NR. 01/05 BLE PATENT NR 313124 FEILAKTIG KUNNGJORT TRADT UT AV KRAFT PATENTET ER FORTSATT I KRAFT.)
2005-01-03	MM1K -	Lapsed by not paying the annual fees

HU9402807A0.

Gazette date	Code	Description (remarks) List all possible codes for HU
2006-06-28	TH4A	Erratum

HU9401478A0:

Gazette date	Code	Description (remarks) List all possible codes for HU
1998-01-28	DFC4	Cancellation of temporary prot. due to refusal

HU0218673B:

Gazette date	Code	Description (remarks) List all possible codes for HU
2006-06-28	TH4A	Erratum

HU0075703A2:

Gazette date	Code	Description (remarks) List all possible codes for HU
1998-01-28	DFC4	Cancellation of temporary prot. due to refusal

HU0074916A2:

Gazette date	Code	Description (remarks) List all possible codes for HU
2006-06-28	TH4A	Erratum

HK1005687A1:

Gazette date	Code	Description (remarks) List all possible codes for HK
2004-12-15	PF +	Patent in force

HK1005686A1:

Gazette date	Code	Description (remarks) List all possible codes for HK
2004-12-15	PF +	Patent in force

GB2288117A:

Gazette date	Code	Description (remarks) List all possible codes for GB
1996-07-31	WAP -	Application withdrawn, taken to be withdrawn or refused ** after publication under section 16(1)

GB2287880A8:

Gazette date	Code	Description (remarks) List all possible codes for GB
1996-07-24	WAP -	Application withdrawn, taken to be withdrawn or refused ** after publication under section 16(1)

2002-05-08	17P +	Request for examination filed (2001-12-20)
2002-05-08	AK +	Designated contracting states in an application without search report. (AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE)
2002-05-08	AX +	Extension of the european patent to (SI PAYMENT 20011220) (SI PAYMENT 20011220)
2002-05-08	AC	Divisional application (art. 76) of. (EP00630646)

EP0729751TD:

Gazette date	Code	Description (remarks) List all possible codes for EP
2007-08-15	18R -	Refused (2007-05-30)
2005-07-13	RIN1	Inventor (correction) MILLER, RONALD BROWN
2005-07-13	RIN1	Inventor (correction) LESLIE, STEWART THOMAS
2005-07-13	RIN1	Inventor (correction) MALKOWSKA, SANDRA THERESE ANTOINETTE
2005-07-13	RIN1	Inventor (correction) SMITH, KEVIN JOHN
2005-07-13	RIN1	Inventor (correction) WIMMER, WALTER
2005-07-13	RIN1	Inventor (correction) WINKLER, HORST
2005-07-13	RIN1	Inventor (correction) HAHN, UDO
2005-07-13	RIN1	Inventor (correction) PRATER, DEREK ALLAN
2004-01-21	RAP1	Applicant reassignment (correction) (New owner: EURO-CELTIQUE S.A.)
1999-08-11	17Q +	First examination report (1999-06-28)
1997-03-13	DET	DE: translation of patent claims
1996-11-15	EL +	FR: translation of claims filed
1996-10-15	ITCL +	IT: translation for ep claims filed (STUDIO ASSOC MARIETTI & PIPPARELLI)
1996-09-04	17P +	Request for examination filed (1996-02-20)
1996-09-04	AK +	Designated contracting states in an application with search report: (AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE)
1996-09-04	AC	Divisional application (art. 76) of: (EP00699436)

EP0729751A1:

Gazette date	Code	Description (remarks) List all possible codes for EP
2007-08-15	18R -	Refused (2007-05-30)
2005-07-13	RIN1	Inventor (correction) MILLER, RONALD BROWN
2005-07-13	RIN1	Inventor (correction) LESLIE, STEWART THOMAS
2005-07-13	RIN1	Inventor (correction) MALKOWSKA, SANDRA THERESE ANTOINETTE
2005-07-13	RIN1	Inventor (correction) SMITH, KEVIN JOHN
2005-07-13	RIN1	Inventor (correction) WIMMER, WALTER
2005-07-13	RIN1	Inventor (correction) WINKLER, HORST
2005-07-13	RIN1	Inventor (correction) HAHN, UDO
2005-07-13	RIN1	Inventor (correction) PRATER, DEREK ALLAN
2004-01-21	RAP1	Applicant reassignment (correction) (New owner: EURO-CELTIQUE S.A.)
1999-08-11	17Q +	First examination report (1999-06-28)
1997-03-13	DET	DE: translation of patent claims
1996-11-15	EL +	FR: translation of claims filed
		IT: translation for ep claims filed (STUDIO ASSOC MARIETTI